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RIBOFLAVIN DEFICIENCY IN MAN*

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SINCE 1933 we have observed in 15 patients the characteristic skin and mucous membrane lesions now believed to be a manifestation of riboflavin deficiency. At first we thought that these lesions were uncommon manifestations of pellagra. After Sebrell and Butler[1] had experimentally produced similar lesions in human beings and cured them with synthetic riboflavin, we recognized and proved the true nature of the condition.

Riboflavin, the accepted[2] name for vitamin B_2, described[3] chemically as 6, 7-dimethyl-9-(d-1′-ribityl)-iso-alloxazin, is a necessary constituent in the diet of many animals. In the rat its lack leads to a failure in growth, senility, alopecia, a nonspecific dermatitis and cataract formation; in the dog an acute deficiency[4] leads to spasticity, generalized weakness, circulatory collapse and a "yellow" liver, while a chronic partial deficiency[5] results in signs characterized clinically by ataxia. Although riboflavin is presumably present in every living cell and is concerned with the chemical reactions involved in cell respiration,[3] no distinct clinical syndrome in man had been attributed to its deficiency prior to Sebrell and Butler's[1] report.

The lesions produced by Sebrell and Butler in 10 of 18 women maintained on the diet of Goldberger and Tanner‖ appeared ninety-four to one hundred and thirty days after the beginning of the experiment. They began

> as a pallor of the mucosa of the lip in the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, and within a few days superficial transverse fissures appeared, usually bilateral, and exactly in the angle of the mouth. These fissures extended somewhat downward from the angle. . . . In some instances the fissures continued to extend onto the skin for a distance of as much as half an inch. These lesions resemble those described as perlèche. At about the time the fissures were seen, the lips became abnormally red along the line of closure. This was due apparently to a superficial denudation of the mucosa. In addition to the cheilosis, there was also seen a fine, scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the alae nasi, in the vestibule of the nose and on the ears.

Under the conditions of the experiment these lesions were alleviated by the administration of synthetic riboflavin, but not by nicotinic acid. The authors' conclusion that the condition is a manifestation of riboflavin deficiency seems warranted. Since then, Oden, Oden and Sebrell[6] have reported 3 patients from rural Georgia with similar lesions which responded promptly to 5 mg. of synthetic riboflavin given daily. They believe, since the Odens have seen many similar cases in their practice in rural Georgia, that ariboflavinosis is in all probability a common deficiency disease in the southern United States. Sydenstricker[7] thinks that these lesions are "even more frequent than frank pellagra."

The first patient in whom we recorded the occurrence of these lesions presented such a unique dermatosis that in subsequent cases such lesions were designated by his name. Fifteen patients with similar lesions have been observed: 6 men, from thirty to thirty-eight years of age, and 9 women, from twenty-five to fifty. Thirteen were alcohol addicts, 1 had advanced pulmonary and intestinal tuberculosis and 1 was an epileptic. In addition to riboflavin deficiency 5 patients had pellagra, 5 pellagra and polyneuritis, 1 pellagra, polyneuritis and scurvy, 2 pellagra and scurvy and 1 polyneuritis; 1 patient showed no manifesta-

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‖This diet consisted of cornmeal, grits, wheat flour, rice, sweet potatoes, cabbage, collards, fat pork, lard, cane syrup, sugar and vitamin-free casein.

tions of other deficiency disease. The series therefore includes 13 cases of pellagra, 7 of polyneuritis and 3 of scurvy. The facial lesions seen consisted of filiform excrescences of a seborrheic nature, apparently derived from the sebaceous glands and varying in length up to 1 mm., closely to sparsely scattered over the skin of the face. Their characteristic location was in the nasolabial folds, but in addition they occurred frequently on the alae nasi, occasionally on the bridge of the nose and sometimes on the forehead above the eyebrows. The skin on which the excrescences were located was the seat of a fine, scaly, greasy desquamation. On casual inspection these filiform lesions resembled urea frost, but they could not be brushed off by rubbing with the fingers. In addition most of the patients showed fissures and maceration at the angles of the mouth, and a degenerative, crust-like formation on the epithelium of the lips, most marked on the lower. The fissures at the angles of the mouth were bilateral and extended laterally 1 to 3 mm. onto the mucous membrane of the mouth and 1 to 10 mm. onto the skin. They were usually very shallow but were sometimes 0.5 mm. deep, and their bases as a rule showed little or no increased redness. Extending for 5 to 20 mm. from the angle of the mouth onto both lips, the mucous membrane was macerated and wrinkled and pearl-gray. The lips, particularly the lower, frequently showed a marked increase in the vertical fissuring, often without a break in the mucous membrane. Occasionally the vestibule of the nose was involved, with lesions similar to those on the lips. We observed no lesions on the ears.

Our first 10 subjects, all of whom were pellagrins, were maintained on the diet of Goldberger and Tanner. After a control period of three to fifteen days, during which neither the facial lesions nor the cheilosis improved, various preparations then being tested for their value in the treatment of pellagra were given. Preparations which produced a cure of the stomatitis of pellagra were followed also by disappearance of the facial and lip lesions now ascribed to riboflavin deficiency.* These were Vegex, brewers' yeast and liver residue. Highly concentrated liver extract effective in pernicious anemia, cod-liver oil, linseed oil, cevitamic acid and thiamin chloride were ineffective not only in pellagrous stomatitis but also on these facial and lip lesions. For this reason we believed that the lesions were all part of pellagra. The following case report, in addition to describing the first case in which these distinctive lesions were recognized, is fairly representative of the 10 cases in which the lesions responded to Vegex, brewers' yeast or liver residue.

*The synthetic riboflavin, thiamin chloride and cevitamic acid used in this study were supplied by Merck and Co., Rahway, N. J.; the nicotinic acid by Merck and Co., and by the S.M.A. Corporation, Chicago; the Vegex and brewers' yeast by Vegex, Inc., New York City; the liver residue by Lederle Laboratories, Inc., New York City.

Case 1. L. P., a 35-year-old, white, alcoholic vagabond, was admitted to the Medical Service of the Psychiatric Division of Bellevue Hospital on June 25, 1933, complaining of a sore mouth, diarrhea and dermatitis. He had been drinking heavily and eating little and irregularly for at least 3 months. Mentally he presented a Korsakoff psychosis. Physically he had a pellagrous dermatitis of the hands, stomatitis, glossitis, diarrhea, normocytic anemia and peripheral neuritis. He was maintained on a diet poor in the vitamin B complex plus cod-liver oil; after 1 week he was given in addition, by parenteral injection, a concentrated liver fraction effective in pernicious anemia, 9 cc. daily for 7 days, and thereafter 3 cc. daily. This was followed by slight improvement in the dermatitis of the hands and in the anemia, but at the end of 42 days no improvement was noted in the glossitis, stomatitis, diarrhea or peripheral neuritis. At this time we observed an unusual lesion on the patient's face. It consisted of fine filiform seborrheic excrescences about 0.5 mm. in length, distributed in the nasolabial folds, on the alae nasi, on the bridge of the nose and on the forehead above the eyebrows. The liver extract was discontinued and the patient was thereafter maintained on the same diet, plus 18 gm. of Vegex by mouth daily. Within a week the glossitis, stomatitis and diarrhea disappeared and the peripheral neuritis and dermatitis of the hands improved; it was not until the 18th day of this regimen, however, that a significant improvement was noted in the lesions about the nose and forehead. From this time on the facial lesions rapidly improved, so that by the 34th day of treatment they had completely disappeared. The Korsakoff psychosis remained, however, and the patient was committed to a state hospital for the insane.

The appearance of the facial lesion while the patient was under observation and being maintained on a diet poor in the vitamin B complex, the failure of cod-liver oil to prevent its development and its cure following the addition of Vegex to the same diet led us to believe that it was a manifestation of deficiency in some fraction of the vitamin B complex. Since the recognized pellagrous lesions of stomatitis, diarrhea and dermatitis were simultaneously though more rapidly cured, we believed that this lesion was one of the less common manifestations of pellagra.

The results in this case were confirmed in 9 subsequent cases which showed the same distinctive lesions. When, however, we began the treatment of our pellagrins with nicotinic acid while still maintaining them on the diet poor in the vitamin B complex, although we obtained dramatic responses in the oral, gastrointestinal and mental manifestations of pellagra, the facial and lip lesions were not affected. After the response to nicotinic acid, 2 of these patients were given a full diet supplemented with 18 gm. of Vegex daily by mouth. The characteristic facial and lip le-

sions promptly responded. The following case is illustrative.

Case 2. D. G., a 31-year-old, unemployed, alcoholic Negro, was admitted to the Medical Service of the Psychiatric Division on December 8, 1938, complaining of anorexia and fatigue of many weeks' duration and a sore tongue and mouth of 1 week's duration. He gave a history of drinking at least 1½ pints of whisky daily for many years; about 4 weeks before admission he had increased his whisky intake and reduced his food consumption to practically nothing.

Physical examination revealed the following significant findings. There was a nystagmus on lateral gaze. The patient had difficulty in opening his mouth because of pain. The tongue was scarlet red, and the papillae were almost completely absent. The buccal mucous membrane was similarly reddened. In addition there were a few small,

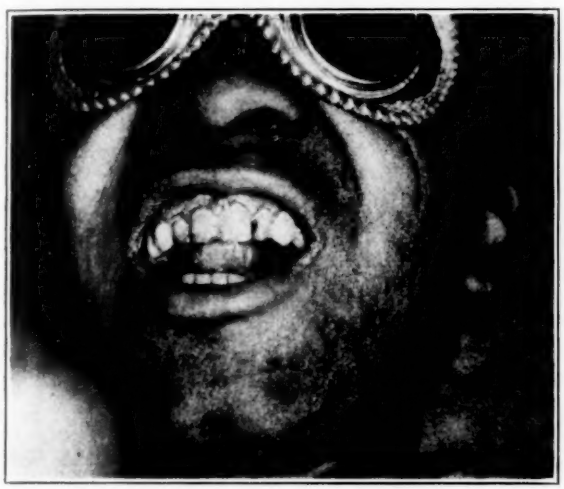

Figure 1. *Patient D. G. (before treatment).*

superficial, pearl-gray ulcerations on the buccal mucous membrane opposite the molar teeth and on the floor of the mouth. At the angles of the mouth there were fissures and maceration (Fig. 1). The lower lip showed cracking and degeneration of the superficial epithelium. Across the bridge of the nose and in the nasolabial folds, extending onto the cheeks and less so across the forehead, were greasy filiform excrescences. There was an acute balanitis, the color being identical with that of the mucous membrane of the mouth. A mild peripheral neuritis was present, but there was no dermatitis of the hands, feet, perineum, elbows or neck.

The patient was maintained on the diet poor in the vitamin B complex. On the 6th hospital day the stomatitis and balanitis were worse; the filiform lesions in the nasolabial folds and the fissures and maceration at the angles of the mouth were unchanged. For the next 4 days, ten doses of 100 mg. of nicotinic acid were given daily by mouth. Improvement in the stomatitis and balanitis was noted within 24 hours; by the end of the 4th day of nicotinic acid therapy (10th hospital day) the oral and penile lesions had completely healed. The fissures and maceration at the angles of the mouth and the filiform dermatitis, however, were unchanged, and the peripheral neuritis had grown worse. The patient was then given a vitamin-rich diet, plus 18 gm. of Vegex by mouth and 20 mg. of thiamin chloride by intramuscular injection daily. The peripheral neuritis improved, and in 14 days the filiform excrescences and the fissures and maceration had disappeared.

While this patient was on the ward, but after the regimen of the vitamin-rich diet with the supplements had been started, Sebrell and Butler's[1] report appeared. Their description of the lesions which they had produced experimentally suggested to us that the lesions we had been observing in our subjects were probably signs of more advanced states of riboflavin deficiency. If true, this observation would explain their failure to respond to nicotinic acid and their response to a full diet plus Vegex, brewers' yeast or liver residue, substances rich in riboflavin. We therefore determined to test the effect of synthetic riboflavin on the lesions occurring in our subjects. Since then we have observed 3 more such patients, 2 women and 1 man. Two of these cases are reported in detail. The third patient, a young Negress with widespread pulmonary and gastrointestinal tuberculosis who had a typical nasolabial filiform dermatitis and lip lesions, died of tuberculosis before the effect of the treatment with riboflavin could be demonstrated.

Case 3. J. B., a 45-year-old, alcoholic Negro painter, was admitted to the Medical Service of the Psychiatric Division on March 24, 1939, complaining of soreness of the

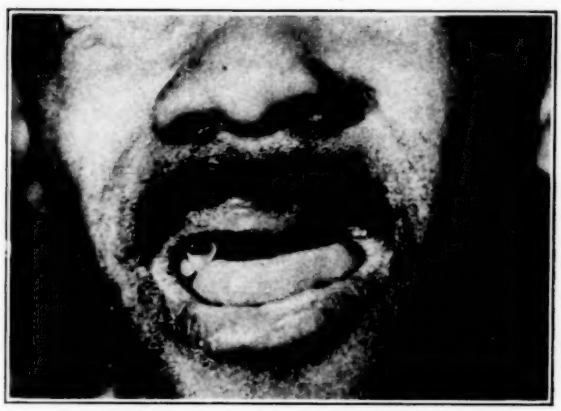

Figure 2. *Patient J. B. (before treatment).*

mouth and throat, soreness in the vestibule of the nose, a "breaking out of the skin," weakness and difficulty in walking for 1 month. He gave a history of long indulgence in whisky up to the onset of the symptoms. During the previous few months he had eaten little and irregularly, meat, milk, eggs and vegetables being excluded from his diet. After the onset of the symptoms he had discontinued alcohol and subsisted on soups.

Physical examination revealed the following significant findings. There was a bilateral nystagmus on lateral gaze. The tongue (Fig. 2) was smooth and slightly fissured and moderately red, with ulcerations on the tip and frenulum covered with a pearl-gray exudate. The oral mucous membranes showed abnormal redness. On the floor of the

mouth there were ulcerations and exudate similar to those on the tongue. The lower lip showed degeneration of the epithelium with crusting and scaling. There were fissures at the angles of the mouth extending about 5 mm. from the angles onto the skin of the face. In this area there was considerable maceration and a grayish, moist slough, distinctly noticeable in Figure 2. The upper lip was normal except for a slight increase in the horizontal fissures. On both alae nasi (Figs. 2 and 3), and especially prominent in the nasolabial folds, were heaped-up, seborrheic excrescences consisting of tightly packed filiform projections.

FIGURE 3. *Patient J. B. (before treatment).*

Inside the nares (Fig. 3) was seen a crusted, elevated exudate not easily removable. Over both hands and elbows there was a dry, chronic, pellagrous lesion, and the skin of the groin and perineum was rough, pigmented and moderately reddened. There was no evidence of peripheral neuritis. Diagnoses of riboflavin deficiency and nicotinic acid deficiency were made.

Within an hour after admission the patient was seen by Dr. W. H. Sebrell, who expressed the opinion that these lesions were those of riboflavin deficiency, more advanced than those produced by Sebrell and Butler experimentally.

The patient was maintained on the diet poor in the vitamin B complex, plus 200 cc. of 5 per cent glucose in physiologic saline solution, given by mouth every hour for the first 2 hospital days. On the 3rd and 4th days, without change of diet, he was given 50 mg. of synthetic riboflavin per day intramuscularly, and thereafter 10 mg. daily by mouth. By the 5th day definite improvement was noted in the fissures at the angles of the mouth (Fig. 4); their depth was not so great and the maceration was almost healed. The lesions in the nasolabial folds and nares also showed a decrease in the degree of heaping up of the filiform excrescences, and the degeneration of the epithelium of the lower lip was much lessened. While these lesions were clearing, the oral lesions involving the tongue, floor of the mouth and buccal mucous membranes grew worse, with an increase in redness and ulcer formation; a moderately severe diarrhea also developed. It was deemed inadvisable to withhold nicotinic acid therapy for these pellagrous lesions. Continuing the same regimen, the patient was given in addition 1000 mg. of nicotinic acid per day orally in divided doses for 3 days. Rapid cessation of the diarrhea and healing of the dermatitis followed. Meanwhile the nasolabial dermatitis and the lesions of the lips and angles of the mouth continued to improve.

On the 12th hospital day the patient developed signs of mild peripheral neuritis. This condition responded promptly to the administration of thiamin chloride in doses of 10 mg. per day intramuscularly for 3 days. On the 17th day the lesions in the nasolabial folds were almost entirely healed, only a small pigmented area without heaped-up excrescences remaining. The deep fissuring at the angles of the mouth and between the nares and upper lip was healed and the epithelium of the lips was normal. The lesions in the perineum had entirely healed, and the old chronic pellagrous lesions of the hands and elbows were gradually clearing. From the 18th day the patient was given a diet rich in vitamin B, plus 18 gm. of Vegex daily, other supplements being discontinued. He was discharged on the 40th day.

CASE 4. V. B., a 34-year-old, white woman, was transferred from an institution for the care of epileptics, where she had been a patient for the previous 5 years, to the Medical Service of the Psychiatric Division on January 28, 1939. She complained of weakness, bleeding gums, sore mouth and a rash on the face and hands of a few weeks' duration. The history included epileptic convulsions since the age of 3, a craniotomy in 1932 without improvement in the convulsions and an appendectomy in 1921. Her diet (as eaten by the patient) had consisted chiefly of the following: breakfast, oatmeal, coffee and white bread;

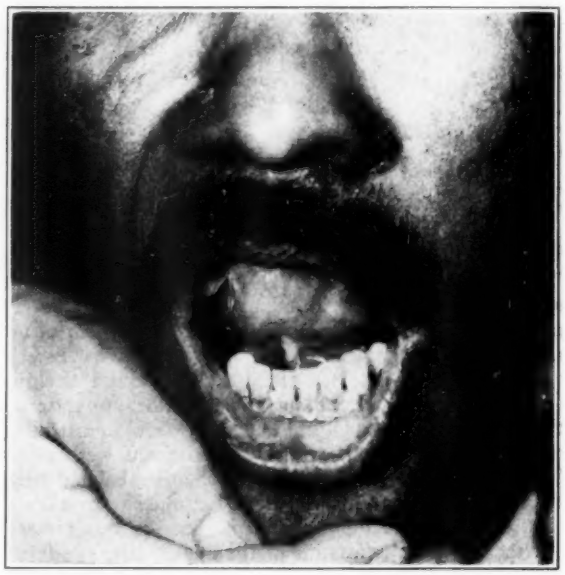

FIGURE 4. *Patient J. B. (after five days of riboflavin therapy).*

lunch, white bread and butter, potatoes and a portion of stew; supper, tea, white bread and butter, prunes and apricots. She received one egg per week. She never ate the meat in the stew but gave it to others. She consumed daily large amounts of cake furnished by her parents, so that the main constituents of her diet were cake and white bread.

Physical examination disclosed a thin, undernourished, well-oriented and co-operative woman. There was a bilateral nystagmus on lateral gaze. The lower lip showed degeneration, with scaling and desquamation of the epithelium. There were fissures at the angles of the mouth.

A seborrheic lesion consisting of filiform excrescences about 0.5 mm. in length, appearing to protrude from the sebaceous glands, was present in the nasolabial folds and across the bridge of the nose. The lesion superficially resembled urea frost but could not be rubbed off, and the underlying skin felt greasy. It was not present on the upper lip, vestibule of the nose, forehead or ears. In addition there was an acneform eruption over the face, which was so prominent as to hide most of the filiform lesions. The upper jaw was edentulous. The gums of the lower jaw were red and markedly piled, with bags of blood around the teeth; they bled at the slightest touch. The tongue was clean, bald and slightly reddened, as were the mucous membranes. Along the frenulum a pearl-gray ulceration was present. On the right hand there was deep pigmentation over the second interphalangeal joint and thumb, a small amount of ulceration over the knuckles and a bracelet-like, pigmented dermatitis of the wrist. The left hand exhibited a bracelet-like, pigmented dermatitis and a slight dermatitis over the second interphalangeal joint. There was increased keratosis of the elbows. There were no "necklace lesions" and no perineal lesions. There was no evidence of peripheral neuritis. Diagnoses of riboflavin, nicotinic acid and cevitamic acid deficiencies and epilepsy were made.

The patient was maintained on the diet poor in the vitamin B complex. Studies of the blood revealed total absence of cevitamic acid. The patient was given 300 mg. of cevitamic acid daily by intravenous injection, and 100 mg. four times daily by mouth. On the 3rd hospital day there was definite improvement in the gums in that redness was decreased and they bled less readily on pressure. On the following day the gums were natural in color except for a small area adjacent to one of the incisors, which was still reddened but did not bleed. The dose of cevitamic acid was reduced to 200 mg. daily by mouth. The stomatitis and glossitis remained unchanged. From the 6th hospital day the patient was given 500 mg. of nicotinic acid daily in doses of 100 mg. by mouth. By the 8th hospital day the abnormal redness of the tongue and mucous membranes of the mouth had disappeared, the frenulum ulcer had healed and the dermatitis of the hands was clearing. The lesions on the face and lips, however, were unchanged.

At this time the patient was seen by Dr. V. P. Sydenstricker, who expressed the opinion that the filiform lesions of the face and the lesions in the angles of the mouth and lips were due to riboflavin deficiency.

After 11 days of nicotinic acid therapy and the diet poor in the vitamin B complex there seemed to be no significant change in the filiform lesions on the face or the lip lesions. Beginning on the 17th hospital day, administration of nicotinic acid was discontinued, and 10 mg. of synthetic riboflavin was given daily by mouth. On the 5th day of this regimen a marked improvement was noted. The degenerative epithelial lesion of the lips and the fissures at the angles of the mouth had cleared entirely, the filiform lesions on the nasolabial folds and the bridge of the nose had disappeared and the acneform rash had improved. The patient, however, showed distinct signs and symptoms of mild peripheral neuritis. She was given 50 mg. of thiamin chloride daily by intramuscular injection. This was followed by complete disappearance of the signs and symptoms of peripheral neuritis within 3 days. From the 27th hospital day the patient was maintained with the regular ward diet, supplemented by 200 cc. of orange juice and 18 gm. of Vegex daily, the administration of synthetic riboflavin, cevitamic acid and thiamin chloride being discontinued. The strength of the patient markedly improved, and her weight, then 84 pounds, had increased to 111 pounds when she was discharged on the 53rd hospital day.

These 2 cases proved that the filiform facial lesions and the lip lesions which we had previously noted could be cleared by Vegex, brewers' yeast or liver residue, but not by nicotinic acid, would heal on the administration of synthetic riboflavin. The response was obtained in 1 case before nicotinic acid was administered and while the signs of nicotinic acid deficiency were progressing; in the other case the signs of nicotinic acid deficiency were first cured by nicotinic acid, and subsequent administration of synthetic riboflavin cured the filiform dermatitis and the lip lesions.

DISCUSSION

We believe that the lesions described in this paper represent more advanced lesions of the same etiology as those experimentally produced and described by Sebrell and Butler.[1] The only difference is the presence of the filiform lesions in our subjects, but these occur on the same fine, scaly, slightly greasy base, in the same distribution and associated with the same lip lesions as in the cases produced experimentally. Furthermore, the non-experimental lesions of our patients responded to the same therapeutic test as did the experimental lesions of Sebrell and Butler. Neither our lesions nor theirs were improved by nicotinic acid; both responded to riboflavin, whether given in its natural form, as contained in Vegex, brewers' yeast or liver residue, or in its synthetic form.

It is interesting to note that 13 of our 15 patients showed in addition signs of nicotinic acid deficiency and 7 showed signs of thiamin deficiency. Spies and his associates[8] reported 40 patients with riboflavin deficiency as manifested by lesions similar to those reported by Sebrell and Butler. About half their subjects also had pellagra. The coexistence of these deficiencies is not an unexpected phenomenon, since these three vitamins are with a few exceptions distributed in the same foodstuffs. This suggests that in patients manifesting a clinical deficiency of any one vitamin, other fractions of the vitamin B complex, whether known or not as yet chemically identified, or other accessory elements of nutrition may also be playing a role in the production of symptoms. This experience is illustrated in Case 4. In this case, scurvy was cured by cevitamic acid, pellagra was cured by nicotinic acid, filiform face lesions and cheilosis were cured by synthetic riboflavin, and polyneuritis, which developed while the patient was being maintained with the diet poor in the vitamin B complex, was cured by thiamin chloride. On the other hand, the patient failed to gain weight or strength, and her

acne did not completely disappear until she was given a vitamin-rich diet supplemented with Vegex.

It is probable, as Vilter, Vilter and Spies[9] have suggested, that other manifestations hitherto considered a part of the pellagra syndrome are also due to riboflavin deficiency. Four endemic pellagrins maintained by them with a pellagra-producing diet and supplements of nicotinic acid and thiamin showed rapid improvement, but when continued on the same regimen these patients began to lose appetite and weight, and the investigators observed the appearance of what they described as a mild dermatitis. They then administered riboflavin to these patients and observed improvement within forty-eight hours, although the dermatitis appeared to be more chronic than the characteristic pellagrous dermatitis.

An interesting phenomenon in our cases of riboflavin deficiency was the preponderance of women over men. Nine (60 per cent) of our 15 patients with riboflavin deficiency were women, while only 26 per cent of the pellagrins routinely admitted to this service are women and the ratio of men to women admitted is 6:4. Spies and his associates[8] have also seen this deficiency most frequently in women, and in all 3 cases reported by Oden, Oden and Sebrell[6] the patients were women.

The nonexperimental cases of riboflavin deficiency in man seen by Oden, Oden and Sebrell[6] and by Spies and his associates[8] have occurred in the South, where pellagra is endemic. The fact that 10 cases were recorded by us in New York City before we recognized the true nature of the lesions, and the fact that since Sebrell and Butler's[1] report we have seen an average of 1 case per month on this service, while the average admissions were 272 per month, indicate, however, that the disease may be not uncommon in the northeastern states. This seems to be more likely in view of the now recognized frequency in this area of the lesions due to other fractions of the vitamin B complex, and the generally coincident distribution of those nutritional elements with riboflavin in foodstuffs.

SUMMARY AND CONCLUSIONS

We have described lesions in 15 patients which are similar to, though more advanced than, those produced experimentally by Sebrell and Butler. These lesions consist of filiform, seborrheic excrescences distributed most often in the nasolabial folds but frequently involving the alae nasi and less often the bridge of the nose and the forehead, superimposed on a skin which has a fine, scaly, greasy desquamation in the same locations, and cheilosis, characterized by maceration and fissures at the angles of the mouth and degeneration of the epithelium of the lips, especially the lower.

These lesions, like those produced experimentally, improve following the administration of natural or synthetic riboflavin, but fail to respond to diets poor in the vitamin B complex or to nicotinic acid. We therefore feel justified in attributing them to riboflavin deficiency.

REFERENCES

1. Sebrell, W. H., and Butler, R. E.: Riboflavin deficiency in man; preliminary note. Pub. Health Rep. **53**:2282-2284, 1938.
2. Report of Council on Pharmacy and Chemistry. Riboflavin, the accepted name for vitamin B_2. J. A. M. A. **108**:1340, 1937.
3. Booher, L. E.: Chemical aspects of riboflavin. J. A. M. A. **110**:1105-1111, 1938.
4. Cowgill, G. R.; Zimmerman, H. M., and Burack, E.: Studies of vitamin G (B_2) deficiency in dogs: preliminary communication. Am. J. Physiol. **109**:24, 1934.
   Street, H. R., and Cowgill, G. R.: Acute riboflavin deficiency in the dog. Am. J. Physiol. **125**:323-334, 1939.
   Sebrell, W. H., and Onstott, R. H.: Riboflavin deficiency in dogs. Pub. Health Rep. **53**:83-94, 1938.
   Sebrell, W. H.; Onstott, R. H., and Hunt, D. J.: The treatment of blacktongue with a preparation containing the "filtrate factor," and evidence of riboflavin deficiency in dogs. Pub. Health Rep. **52**:427-433, 1937.
5. Cowgill, G. R.: personal communication.
6. Oden, J. W.; Oden, L. H., and Sebrell, W. H.: Report of three cases of ariboflavinosis. Pub. Health Rep. **54**:790-792, 1939.
7. Sydenstricker, V. P.: personal communication.
8. Spies, T. D.: personal communication.
9. Vilter, R. W.; Vilter, S. P., and Spies, T. D.: Relationship between nicotinic acid and a codehydrogenase (cozymase) in blood of pellagrins and normal persons. J. A. M. A. **112**:420-422, 1939.

THE ETIOLOGY AND PATHOGENESIS OF THYROTOXICOSIS, WITH SPECIAL REFERENCE TO ITS PITUITARY ORIGIN*

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LWÓW, POLAND

THE etiology and pathogenesis of thyrotoxicosis have an enormous literature, and continue to be subjects of considerable controversy. In considering the gradual alteration of opinions concerning these subjects, we should look on them from a double point of view; that is to say, intrinsic and extrinsic factors should be differentiated.

Intrinsic Factors

The intrinsic abnormality of the thyroid gland which would cause thyrotoxicosis would be a condition in which the gland has primarily lost its ability to retain the elaborated hormone. Such a condition represents a sort of "thyroid diarrhea," as Kocher† called it, which permits, or occasions, an excessive escape of thyroid hormone into the blood stream. Indeed, Wilson and Kendall (1916) were the first to prove that the amount of thyroxine in the thyrotoxic gland is smaller by one fifteenth or one twentieth than the amount in the normal thyroid gland. They interpreted it as a result of increased secretion into the circulation. This is in line with the increase in total blood iodine (Veil and Sturm, 1925; Lunde et al., 1929; Curtis et al., 1933), in direct relation with that of thyroxine (Elmer, Rychlik and Scheps, 1934). The last-named writers found the thyroxine-iodine level in blood to be elevated, ranging from 8 to 16 micromg. per 100 cc., while normally it varies between 3 and 5. Naturally the total blood iodine level is much greater. In agreement with this, we (1933) found the iodine elimination in urine and bile greater in patients with thyrotoxicosis than in normal individuals. Curtis and his associates (1934) and Scheffer (1937) went farther in this matter by determining the iodine elimination in the feces, by the skin and by the lungs, thus giving a more complete picture of the increased iodine excretion from a thyrotoxic body. These researches show in thyrotoxicosis a negative iodine balance which in severe cases must naturally lead to the depletion of iodine. It is not surprising that the clinical improvement which has been clear since the introduction of iodine by Plummer and Boothby (1924) may be at least partly explained, outside the inhibiting effect of iodine, by the covering of the increased loss in iodine.

In the secretion of the thyroid hormone, we meet at once the question raised by Moebius (1886), Plummer and others as to whether in thyrotoxicosis a normal or an altered hormone is secreted. The former hypothesis is based, on the one hand, on the relief of thyrotoxicosis produced by iodine treatment, suggesting that a less-iodized hormone is elaborated, and on the other hand, on the much stronger effect of thyroglobulin obtained from thyrotoxic thyroid glands than of that from normal ones. Since Gaddum (1927–1930), Abderhalden and Wertheimer (1928) and Kendall (1931) have shown that thyroxine derivatives containing less iodine produce a much weaker effect than does thyroxine, the first hypothesis of less-iodized hormone is no longer tenable.

With regard to the second possibility, that of secretion of an altered hormone, the great divergence of opinions should be emphasized. These opinions either favor the theory of dysthyroidism (F. Müller, 1927; Cooksey and Rosenblatt, 1928; Saito, 1933; Lerman and Salter, 1934) or undermine it by showing that biologic activity per unit of iodine is even too low in thyrotoxic glands (Krogh and Lindberg, 1932; Palmer and Leland, 1935). Thus the problem of dysthyroidism still remains to be elucidated.

An entirely different view was proposed by Abelin (1932) and later supported by Brugsch (1935). The outcome of Abelin's investigations was the conception that di-iodotyrosine is an antihormone of thyroxine. He suggested that in normal organisms there is an equilibrium between these two hormones, and that in thyrotoxicosis this equilibrium is disturbed by thyroxine's becoming predominant. This hypothesis was supported by the experiments carried out by Abelin and Wegelin (1932). They found that if guinea pigs were given the thyrotropic hormone intraperitoneally, the effect produced on the histological structure of the thyroid gland was reduced or even completely inhibited by simultaneous oral administration of di-iodotyrosine.

Our experiments might confirm Abelin's conclusion that di-iodotyrosine reduces the action of

*Presented at a meeting of the Harvard Medical Society, Boston, April 11, 1939.

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†For a listing of the references, the reader is referred to Dr. Elmer's book *Iodine Metabolism and Thyroid Function* (London: Oxford University Press, 1938).

thyrotropic hormone; nevertheless, they might also show that this inhibitory effect produced by inorganic iodine in equivalent dosage is as great as that of di-iodotyrosine, if not greater. Since inorganic iodine produces the same effect as di-iodotyrosine, the action produced by the latter cannot be regarded as specific. It seems that the inhibitory effect is due merely to iodine released by the breakdown of the di-iodotyrosine in the body. Abelin, however, argued that di-iodotyrosine does not break down in the body, and besides he suggested that the effect produced by potassium iodide is due to the iodine's being synthesized to di-iodotyrosine. In order to ascertain whether the decomposition of di-iodotyrosine takes place, I took 0.2 gm. of di-iodotyrosine (116 mg. of iodine) by mouth and found that it broke down rapidly, since inorganic iodine could be demonstrated in the urine in the first hour, and 57 mg. of inorganic iodine, that is, half of the ingested di-iodotyrosine iodine, was recovered in the twenty-four-hour urine. It appears also from more recent experiments of Snapper and Grünbaum (1937) that the *o*-di-iodophenolic group is not responsible for the inhibitory effect on the thyroid gland, since *n*-benzoyl-di-iodotyrosine, which as is known does not break down in the body, has no influence on the condition of patients with thyrotoxicosis.

Thus it appears that there is no justification in accepting the hypothesis either of the existence of di-iodotyrosine as an antihormone of thyroxine, or of the disturbance in thyroxine–di-iodotyrosine equilibrium as a primary cause of thyrotoxicosis.

Extrinsic Factors

Most probably extrinsic factors play an important part in the etiology and pathogenesis of thyrotoxicosis. It is known that the thyroid gland is subordinated in its activity to the anterior pituitary, and possibly indirectly or directly to the nervous system; moreover, it is correlated with adrenal cortex, sex glands and liver.

The Role of the Adrenal Cortex

The experiments of Marine and his associates (1930) led them to advance the hypothesis that in thyrotoxicosis the fundamental disturbance is due to primary insufficiency of the adrenal cortex. The loss of the control over the oxidative processes occurring in deficiency of function in the suprarenal cortex might result in a physiologic attempt at compensation by an overproduction of thyroid hormone. This seemed to follow from the experiments of Marine and Baumann (1932), who found in rabbits and cats after sublethal injury of the adrenal cortex a transient complex of symptoms which closely resembled thyrotoxicosis. In agreement with this, small suprarenals have usually been found in thyrotoxicosis by Marine (1930).

Now the question arises whether the activity of the adrenal cortex on the thyroid gland should be ascribed to the cortin, or to the cevitamic acid, or to the vitamin B complex which is believed to be connected with the adrenal cortex. Marine and his associates attributed a marked significance both to the cortical hormone and to the cevitamic acid. This claim is based on the one hand on the observation made by Marine and Shapiro (1921) that a rapid improvement after oral administration of fresh suprarenal cortex was observed, and on the other hand on the experiments carried out by Marine, Baumann and Rosen (1934) indicating that the cevitamic acid partially inhibits the thyrotropic action of the anterior pituitary extract on the thyroid gland in guinea pigs. With regard to the latter experiments, we (Elmer, Giedosz and Scheps, 1935) can indeed confirm the partial inhibitory effect of cevitamic acid in hyperthyroidism induced by thyrotropic injections in guinea pigs, but no inhibitory effect could be obtained by us (Elmer, Giedosz and Scheps, unpublished data) after treatment either with cortical extract or with synthetic cortin, desoxycorticosterone acetate. We do not wish, however, to deny that the adrenal glands may suffer from pathologic alterations in the course of thyrotoxicosis, and that some symptoms, for example lack of energy and muscle strength, may be due to the loss of the endocrine activity of the cortex. In such cases, of course, cortin may be beneficial in abolishing the above symptoms, but never those of thyrotoxicosis itself. The role of the cevitamic acid seems to be rather a secondary one, owing to its depletion in the adrenal cortex, that is, in the greatest reservoir in the body.

Since the belief in the primary role of cortin and cevitamic acid is hardly probable, it might be expected that the third constituent, riboflavin (Laszt and Verzár, 1935), believed to be essential for the function of the adrenal gland, plays some role in thyrotoxicosis. Some authors have suggested that riboflavin acts as an antagonist to the thyroid hormone (Kühnau and Stepp, 1933), and that its lack is a fundamental factor in the development of thyrotoxicosis. Recently, Hoen and Oehme (1938) have found that vitamin B_2 in small doses prevents the enlargement of the adrenal cortex usually caused by injections of thyroxine.

We carried out experiments bearing on the relation between thyroid and riboflavin. In young guinea pigs treated simultaneously for a week by thyrotropic hormone in doses corresponding to 6 to 50 mg. of dried anterior pituitary powder and

by 1 mg. of crystalline riboflavin, we failed to find any traces of its inhibiting effect either on the hyperfunctioning thyroid gland or on the enlarged adrenal cortex. In view of our experiments, the role of riboflavin in the etiology of thyrotoxicosis should be questioned.

Since we are speaking of vitamins, I may be permitted to dwell briefly on vitamins B_1 and A. Some authors believe that thyrotoxicosis is caused either by hypovitaminosis, due either to a lack of vitamin B_1 (Kühnau and Stepp, 1933) or of vitamin A (Abelin, 1931). In view of the possible role of these vitamins, we (Elmer, Giedosz and Scheps, 1937) have studied the effect of crystalline vitamins B_1 and A on the hyperfunctioning glands of guinea pigs that had been treated by thyrotropic hormone. It seems to follow from our experiments that a close antagonism between the thyroid gland and vitamin B_1 is hardly possible, since we failed to see any inhibitory effect of vitamin B_1 on the gland.

Some authors have focused attention on vitamin A, regarding it as an antagonist to thyroxine (Abelin, 1931; H. Euler and Klussman, 1932). Our own investigations (Elmer, Giedosz and Scheps, 1935) have shown that the administration of vitamin A, at least in huge doses, partly inhibits the action of the thyrotropic hormone on the thyroid gland. But the role of vitamin A appears to be rather secondary. It should be pointed out that the impairment of the liver caused by the thyroid overactivity occurs parallel with the reduction in its reserve supply of vitamin A, 95 per cent of which is normally stored in the liver.

In summary, it can be said that a more or less marked deficiency of the vitamins may appear at the onset of thyrotoxicosis. The hypovitaminoses result either from increased consumption, to some extent proportional to the metabolic level, or from reduced absorption of vitamins, due to the disturbances in the alimentary canal (hypochlorhydria, diarrhea). It is therefore not surprising that the requirement of vitamins is increased in thyrotoxicosis, and their administration is justified in the treatment, but there seems to be no sufficient justification for accepting their primary role in the etiology of thyrotoxicosis. We agree with Means (1937) that vitamins, except perhaps vitamin A, have no marked, if any, effect on the thyroid gland itself comparable with that of iodine.

The Role of the Gonads

There is no doubt that the normal relation between the ovaries and the thyroid gland is very close. This relation is displayed, among other ways, by the quite important iodine content of the ovaries, by the influence of ovariotomy on the iodine in the thyroid gland and blood and by the changes in iodine metabolism which occur at different functional periods of the ovaries, namely during menstruation and pregnancy and at the time of the menopause. In particular, during the menopause, which is not rarely connected with the development of thyrotoxicosis, the blood-iodine level is slightly increased (Jahn and Kesselkaul, 1928). In hyperiodemia, Cucco (1932) sees a manifestation of increased thyroid activity which seems to be confirmed by the depressing effect of ovarian extracts.

According to Levy-Simpson (1937) and Loeser (1938), both estrone and testosterone exert a beneficial effect in some cases of thyrotoxicosis, which might, in our opinion, be attributed to the depressing effect on the pituitary gland rather than to direct action on the thyroid gland. This seems at least to follow from our recent experiments, in which no inhibitory action either of estrone or of testosterone could be demonstrated in guinea pigs injected with thyrotropic hormone (Elmer, Giedosz and Scheps, 1938).

Finally, it should be mentioned that the role of the ovaries must be considered more important than that of the testicles, since thyrotoxicosis appears three to six times more frequently in women than in men.

The Role of the Anterior Lobe of the Pituitary Gland

A new era was opened by Loeb in 1932 with the fundamental discovery of the thyrotropic hormone, and with the reproduction in guinea pigs of all the principal symptoms of Graves's disease. Loeb's insight has allowed him to put forward the bold hypothesis that the action of the anterior lobe is involved in the etiology of thyrotoxicosis, although it may be only one of several factors concerned in this condition. However, there was one serious objection to such a hypothesis, namely the fact, observed by Loeb himself and confirmed later by Collip and Anderson (1934) and many others, that the thyroid gland and the clinical picture of thyrotoxicosis return to their normal state in spite of the continuation of injections of thyrotropic hormone. The development of this resistance to thyrotropic activity raised the hypothesis of antihormones' being normally present in the blood and counteracting the action of thyrotropic hormone (Collip and Anderson, 1934). We shall not discuss here the great divergence of opinions in explanation of the development of the refractory state. It should be pointed out only that Loeser (1937) has shown that the refractoriness does not appear if continuously increasing

large doses of thyrotropic hormone are administered to guinea pigs.

Attempts to overcome this difficulty and to produce maintained experimental hyperthyroidism have been made by us in dogs and guinea pigs (Elmer, Giedosz and Scheps, unpublished data). Five dogs varying between 4.5 and 6.5 kg. in weight were treated with daily intravenous injections of thyrotropic hormone in continuously increasing doses, together with 0.15 to 2.0 gm. of dried cattle anterior-pituitary powder per kilogram of body weight, for five or six weeks. In all 50 to 150 gm. of anterior-pituitary powder was injected into a single dog. Six young guinea pigs weighing 180 to 200 gm. were treated with thyrotropic hormone in increasing large doses for five or six weeks, during which time 5.5 to 7.5 gm. of dried anterior-pituitary powder was used.

The thyrotropic hormone was prepared by us according to Loeb's acid method. In order to avoid some difficulties in injecting large volumes of pituitary extract, we concentrated it ten to twenty fold to a small volume by ultrafiltration at ice temperature, so that 1 cc. of extract corresponded to 0.5 to 1.0 gm. of anterior-pituitary powder.

We succeeded in obtaining maintained experimental hyperthyroidism in all dogs and guinea pigs. The thyrotoxic condition was manifested by nearly all signs of thyrotoxicosis: general weakness and nervousness, loss in weight, dehydration, polyuria, rise in temperature, marked heart symptoms, increase in basal metabolic rate, hyperiodemia, increased iodine excretion in the urine and hypocholesterolemia with disturbance in estrification. Other symptoms, such as nausea, vomiting, diarrhea and eye signs, were inconstant. All dogs died either during the treatment or seven to ten days after the last injection, having shown general weakness and severe loss in weight. The loss in weight was so great that even increased appetite could not compensate for it. This loss and the slight increase in temperature were probably due to the increased catabolism. Indeed, the basal metabolic rate was always markedly and continuously elevated.

The heart damage was unmistakably evidenced by electrocardiographic changes which should be looked on as specific to a thyrotoxic condition. These often began early, and were comparable in their typical form to those in human thyrotoxicosis. The commonest abnormalities in the electrocardiograms were increases in height of the R and P waves and in depth of S_3, an inversion of T_3 and sometimes the preponderance of the left ventricle. In some dogs only increased P and T waves, which furnish evidence of sympathicotonia, were observed. This typical complex in the advanced course of thyrotropic treatment may change and pass into the electrocardiographic picture which is encountered in coronary insufficiency and sometimes complicates the long-standing onset of human thyrotoxicosis. In agreement with this, we found prominent alterations in the coronary vessels, evidenced by thickening of the walls and narrowing of the lumens. In most of the dogs the heart was enlarged, a phenomenon which was mainly due to hypertrophy of the left ventricle. Histologically there was myocardial damage, manifested by the degeneration of heart muscle (loss of striations and of uniform appearance).

The hypocholesterolemia was very prominent in the second period of the treatment, the value dropping to one third of the original level, that is, from 150 to 50 mg. per 100 cc. The ratio of total cholesterol to cholesterol ester was markedly disturbed, dropping to 25 per cent (normally above 40 per cent), which is evidence of severe injury to the liver. Indeed, histologically the liver showed far-advanced changes: loss of uniform appearance, dissociation of cells and, frequently, fatty degeneration and fatty infiltration. Perhaps to the damaged liver function should be referred the terminal drop of blood sugar (from 110 to 65 mg. per 100 cc.). It should be remarked that liver glycogen was intensively mobilized (0.7 per cent). All this agrees closely with the hypocholesterolemia observed by Hurxthal (1933), and with the frequency of hepatic anatomic changes observed by Beaver and Pemberton (1933) and other authors in human thyrotoxicosis. So it is not surprising that Boothby regards hepatic lesions as an integral part of the syndrome of thyrotoxicosis.

But the most interesting changes were observed in the thyroid glands, which in all the animals appeared histologically to be hyperfunctioning, so that in some cases it was difficult to identify the gland. The histologic aspect falls into line with a high decrease in total iodine, which occurred chiefly at the expense of thyroxine iodine, which decreased from 300 to 400 micromg. per 100 cc. to 40. It can safely be said that the thyroid glands were seriously depleted of thyroxine. A marked hyperiodemia, even to 60 micromg., and increased excretion of iodine in the urine, from 10 to 40 micromg. daily, apply without doubt to this thyroxinorrhea, to which a rise in basal metabolic rate really corresponds.

With regard to other endocrine organs, it should be mentioned briefly that far-advanced changes were observed only in the gonads, particularly in the ovaries, which became highly atresic, and in the anterior lobe of the pituitary gland, which was almost completely deprived of its acidophilic cells.

The disappearance of these cells seems to favor the view that they manufacture the thyrotropic hormone, and it may be regarded as a condition of atrophy from disuse, due to injections of the thyrotropic hormone.

The Role of the Nervous System

The interrelation between the thyroid and anterior pituitary glands on the one hand and the nervous system on the other may be effected either by humoral (blood or lymph) or by nervous paths. Collin (1925) designated as ***hémocrinie générale*** the connection between the pituitary gland and the midbrain by way of the circulation from the anterior lobe veins to the cavernous sinus, and thence by way of the general circulation. In opposition to this general path, there exists a second local circulation which Roussy and Mosinger (1933) called ***hémocrinie locale.*** The anatomical investigations of Popa and Fielding (1930), suggested by Cushing's studies, furnished the basis for accepting a local circulation, a direct vascular link between the pituitary gland and the midbrain, called the "portal" circulation.

Apart from the investigations derived from anatomy, the significance of the nervous system is also shown by certain data based on physiological and pathological researches. Of a number of various attempts which have been made, only some need be mentioned. The higher iodine concentration in the pituitary colloid (1200 to 1300 micromg. per 100 cc., according to Noether, 1932) than in the whole pituitary gland (80 micromg. per 100 cc., according to Sturm, 1928), and also in the midbrain (27 micromg. per 100 cc.) than in the remaining regions of the brain (6 to 9 micromg. per 100 cc., according to Sturm and Schneeberg, 1933), further the drop of the iodine concentration in the midbrain after thyroidectomy and hypophysectomy (Schittenhelm and Eisler, 1933); and finally the rise of iodine concentration in the midbrain and medulla oblongata in animals injected with thyrotropic hormone (Pighini, 1935) and in patients dead from thyrotoxicosis (Sturm and Schneeberg, 1933), all seem to afford the basis for an iodine-regulating center of the midbrain and its etiologic role in thyrotoxicosis. Most probably iodine or thyroid hormone passes in the pituitary colloid from the pituitary gland to the tuber cinereum, which in turn, on being stimulated, may exert an effect through the sympathetic and parasympathetic fibers. In connection with this, it should be mentioned that according to Dobrzaniecki and Aron (1930) the thyrotropic hormone cannot produce a picture of thyroid hyperfunction when the organism is deprived of sympathetic fibers. This suggestion received some support from experiments carried out by Fenz and Uiberrak (1937), which showed the inhibitory effect of midbrain narcosis, produced by the administration of barbiturates, on the thyroid gland in human thyrotoxicosis. These authors found a distinct and often prolonged fall of the increased blood-iodine level normally observed in patients suffering from thyrotoxicosis.

Some other experiments, however, tend to undermine the role of the nervous system. In contrast with Dobrzaniecki and Aron's experiments, Marine and Rosen (1934) have demonstrated on the one hand that thyrotropic hormone stimulates the autothyroid transplants as well. On the other hand, the results of our recent investigations (Elmer, Giedosz, Scheps and Weber, unpublished data) do not fall into line with those of Fenz and Uiberrak. We injected the thyrotropic hormone into guinea pigs intraperitoneally for a six-to-ten-day period and treated them simultaneously with Prominal or Luminal, but we failed to see any inhibitory effects of the barbiturates on the hyperfunctioning thyroid gland. Nevertheless, we agree with Means (1937) that such observations limit rather than exclude a secretory function on the part of the nervous system.

The Role of the Liver

Having described the role of the separate intrinsic and extrinsic factors, I shall now enter into the real pathogenetic mechanism of thyrotoxicosis. Vogt-Moller (1931) in his work on the pathogenesis of thyrotoxicosis stated that the problem raised the question, Is there decrease in the elimination of the thyroid hormone, or in its destruction? This author was rather of the opinion that the alterations in the elimination of the thyroid hormone from the body are the more important in the mechanism of the pathogenesis of thyrotoxicosis. He suggested that the thyroid hormone secreted in excess by the thyroid gland results in damage to the kidneys, which in turn impedes the excretion of the hormone and thereby causes its accumulation in the body. We (Elmer, Giedosz and Scheps, unpublished data) could, indeed, find marked microscopic alterations in the kidneys in experimental permanent hyperthyroidism; but before we can discuss the decrease in urinary thyroxine elimination as a real pathogenetic factor of thyrotoxicosis, it is necessary to show whether the thyroid hormone under physiologic conditions is eliminated in urine. Our investigations afford no basis for belief in elimination of thyroid hormone in this way. Hence, depressed elimination of the thyroid hormone in urine should be discounted as a pathogenetic factor of thyrotoxicosis.

However, the second of the possible pathoge-

netic factors, namely reduced power of destroying the thyroid hormone, seems to play a more important part. Hunt (1907) suggested, as a result of his experiments based on the acetonitrile test, that in thyrotoxicosis there is not only augmented secretion but also diminished destruction of the thyroid hormone in the body. Blum and Grützner (1920) showed that the liver is the organ which possesses the power of destroying the thyroid hormone. Our investigations (Elmer and Luczynski, 1933) seem to point to the conclusion that this power is to some extent limited, even in healthy men, for after excessive administration of the thyroid hormone only a part of it undergoes decomposition. Thus we can easily imagine that in thyrotoxicosis, the increased content of the thyroid hormone in the blood may be due not only to its excessive secretion, but probably also to a slowing up of its decomposition due to diminished activity of the liver in this respect. This supposition receives strong support from a series of clinical and experimental investigations, which give grounds for accepting the view that in thyrotoxicosis the liver undergoes injury under the influence of long-continued secretion of the thyroid hormone in excess. Very remarkable histologic alterations in the liver have been found in human thyrotoxicosis by numerous authors, in particular Beaver and Pemberton (1933). Hepatic injuries are manifested by enlargement or atrophy of the liver, subicterus, a positive galactose test, reduced glycogen content in the liver, hyperketonemia, increased amounts of urobilinogen in the feces and the urine and so forth. In agreement with these observations, the results of our investigations afford the basis for accepting the pathogenetic role of the liver in thyrotoxicosis. In experimental maintained hyperthyroidism we found severe histologic alterations of the liver, which occurred without exception in all animals treated with increasingly large doses of the thyrotropic hormone. The decrease in cholesterol ester in the blood and in glycogen in the liver, observed always in the advanced course of the experimental hyperthyroidism, falls into line with the histopathologic alterations of the liver.

SUMMARY

In the etiology and pathogenesis of thyrotoxicosis both intrinsic and extrinsic factors should be considered.

An intrinsic abnormality of the thyroid gland would be a condition in which the gland either primarily has lost its ability to retain the elaborated hormone or is producing an altered hormone. The conception that in the normal gland there is an equilibrium between thyrotoxine and diiodotyrosine, which in primary hyperthyroidism is disturbed by thyroxine's becoming predominant, lacks any substantial clinical or experimental support.

With regard to the second possibility of the secretion of an altered hormone, the hypothesis of elaborating less-iodized hormone is no longer tenable, and the conception of dysthyroidism, based on the secretion of an otherwise altered hormone, will have to wait upon further experimental evidence.

An extrinsic abnormality of the thyroid would be a condition in which the gland is overproducing the hormone owing to the alterations in other organs. Of many possible extrinsic factors only some play an important part. Evidence for the role of a hyperfunctioning anterior lobe of the pituitary gland in human thyrotoxicosis has been furnished by the author and his associates, who succeeded in inducing an experimental maintained hyperthyroidism in dogs and guinea pigs by injecting the thyrotropic hormone in increasingly large doses.

The significance of the nervous system, in particular of the midbrain, in thyrotoxicosis is also shown by certain data, but its part is limited. The gonads, particularly the ovaries, seem to exert their effect only through the anterior lobe of the pituitary gland. The hypothesis of the primary insufficiency of the adrenal cortex must be rejected.

There is not sufficient justification for accepting the primary role of vitamin deficiency. The hypervitaminoses may result either from secondary increase of the consumption of vitamins or from their reduced absorption due to disturbances in the alimentary canal. The liver damage constantly found in experimental permanent hyperthyroidism and frequently in human thyrotoxicosis plays a very important part in the pathogenesis of thyrotoxicosis. The discrepancy between the excessive production of the thyroid hormone by the thyroid gland and the slowing up of the destruction of the hormone by the liver results in an accumulation of the thyroid hormone in the body, with symptoms of thyrotoxicosis.

PINWORMS AND APPENDICITIS*

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THIS paper presents our conception of the relation of *Enterobius vermicularis* infection‖ of the vermiform appendix to appendicitis in children. That pinworms occur in the appendix has been known for a long time, as Fabricius[1] in 1634 and Sontorini[2] in 1724 described the condition. Only in the last forty years, however, has any active interest been shown in this subject; furthermore, a perusal of the literature leaves one in doubt as to the status of pinworms in relation to appendicitis. The material in this report has been obtained from the 71 cases in which *E. vermicularis* infection was discovered in appendices removed at operation at the Children's Hospital, Boston, from 1929 to 1939.

THE PARASITE

E. vermicularis is a small, white, round worm.[2] The male measures 2 to 5 mm. in length and the female 9 to 12 mm. The worms when young live in the small intestine, but in the adult state they live in the colon. Copulation takes place in the intestine, the gravid female migrating outside the anus or being expelled at defecation. The eggs are deposited outside the host and the female dies. The eggs enter no intermediate host but develop after re-entering a human host. Autoinfection is quite common; there is, however, some evidence[2–4] that reinfection may occur within the gastrointestinal tract. The exact length of the life cycle of the parasite in man is not known; Penso[4] states that it is about twenty days. The diagnosis of pinworm infection is made by finding the worms or ova in the stools, or by finding the ova in anal scrapings or under the fingernails. An intradermal test for pinworm infection has been devised,[5] but its present value is doubtful. Microscopical examination of anal scrapings is the most reliable diagnostic aid.

INCIDENCE

Pinworm infection is very common in children. A recent survey at the Children's Hospital revealed that approximately 18 per cent of the patients harbored pinworms.[6] This rate corresponds roughly to that given in other reports.[7, 8]

In the ten-year period 1929–1939, 1343 appendices were removed at this hospital. Pinworms were found in 71 (5.3 per cent). Beck[9] reports an incidence of 2.0 per cent in 1718 appendices, Gordon[10] 1.2 per cent in 26,051, Goodale[11] 6.1 per cent in 1369, Warwick[12] 1.9 per cent in 2344 and Andrä[13] 6.7 per cent in 2651. It is of interest that in our series the condition was most frequently present in December, January, March and September, and that acute appendicitis was also most frequently seen in those months, with the exception of January.[14]

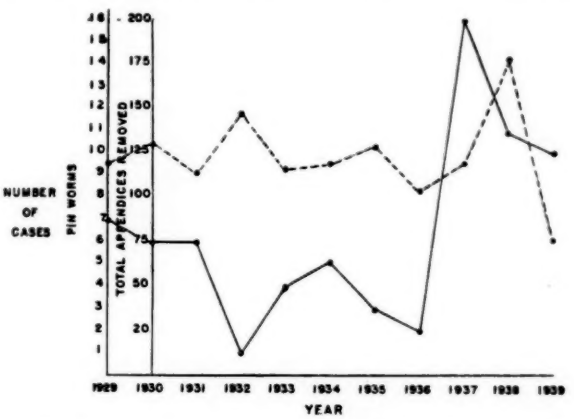

FIGURE 1. —— *Pinworms.* --- *Total appendices removed.*

There has been a marked increase in the number of appendices found to be infected with pinworms during the last three years, although the total number removed each year has been relatively constant (Fig. 1). We believe that the increase is due to a more thorough search for the parasite in the appendiceal contents. This examination consists of a microscopical search as well as a gross inspection. Only by this method can the male

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‖The term "infection" is applicable wherever a parasite invades and establishes itself within the body of the host, including in this sense the gastrointestinal tract.[3]

worm be recognized, whereas the female can be seen with the naked eye. The incidence of appendices containing pinworms would be higher if such a procedure were followed routinely in other hospitals as this figure has more than doubled at this hospital since microscopical examination was included.

Age and Sex

The ages of our patients varied from eighteen months to twelve years. There was a noticeable increase in the number of cases at the age of five and again at the age of eight (Fig. 2). These increases correspond to the ages when children have more opportunity to be infected with the parasites. Girls are more commonly infected than boys.[1, 11] In this series there were 45 girls and 26 boys.

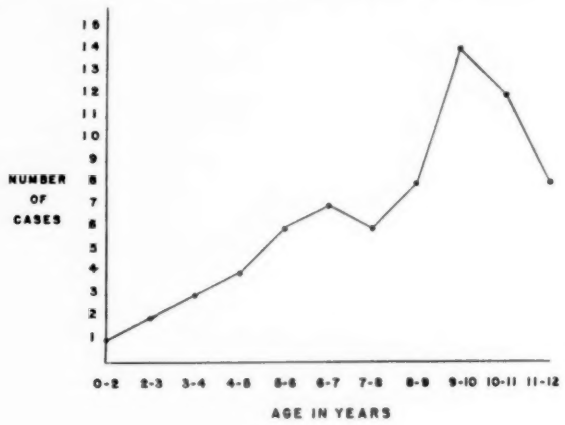

Figure 2.

Clinical Classification

The cases fall naturally into two groups. In Group I are the patients who had acute appendicitis, while Group II includes the cases in which histologic evidence of the condition was lacking. *E. vermicularis* was present in varying numbers in all the appendices of both groups.

Group I

In a total of 848 cases of acute appendicitis, there were 26 appendices containing pinworms. The diagnosis of acute appendicitis was confirmed in all cases by operation or pathological examination, and is the subject of a report by Hudson and Chamberlain.[14]

Twenty-five* patients entered the hospital because of abdominal pain of several hours' to several days' duration (Table 1). The pain was usually referred to the umbilicus and was cramplike. Nausea followed by vomiting was present in 18 cases (69 per cent). In no case was there a history of pinworm infection. Only 7 patients (27 per cent) had had previous attacks of abdominal pain. This corresponds closely to the incidence of previous attacks of pain in children with acute appendicitis without pinworm infection.[14] Those attacks had occurred from one month to one year previously, with most of them two to four months before.

Table 1. *Patients with Acute Appendicitis and* E. vermicularis *Infection.*

Clinical Data	No. of Cases
Previous attacks of abdominal pain	7
No previous attacks of abdominal pain	19
Nausea and vomiting	18
Nausea but no vomiting	5
No nausea or vomiting	3
Tenderness and spasm in right lower quadrant	22
Tenderness but no spasm in right lower quadrant	3
No abdominal tenderness or spasm	1
Temperature (rectal):	
102–101°F.	6
101–100°F.	7
100– 99°F.	13
Leukocyte count:	
25,000–20,000	2
20,000–15,000	6
15,000–10,000	10
10,000– 5,000	5
Not recorded	3

Physical examination revealed tenderness and spasm in the right lower quadrant in 22 cases (95 per cent); in 3 of the remaining 4 cases there was tenderness but no spasm. The leukocyte count was above 10,000 in 18 cases. Search for eosinophilia was not made in any case. In most cases the rectal temperature was between 99 and 101°F.

A diagnosis of acute appendicitis was made and followed by immediate operation in 24 cases. One patient, mentioned above, had been operated on at another hospital. Another did not show sufficient signs on entry to justify the diagnosis; operation was performed two days later and a subsiding appendicitis was found. In 4 cases the appendix had ruptured and peritonitis was present. There were no deaths in this group.

The pathological examination of the appendices revealed no evidence that *E. vermicularis* was the initiating factor.[15] From the clinical aspect the cases did not differ from the usual picture of appendicitis seen in children.[14]

Group II

Of 495 appendices described by the pathologist as presenting no inflammatory reaction, 45 harbored pinworms. Forty-four patients* complained of abdominal pain (Table 2). There was no history of previous pinworm infection in any case. A history of attacks of abdominal pain prior to entry was

*The twenty-sixth patient had had acute appendicitis with peritonitis three months before being admitted for interval appendectomy. At the time of his original illness only incision and drainage of the peritoneal cavity were performed.

*The forty-fifth patient was operated on because of an ovarian tumor and the appendix was removed incidentally.

obtained from 30 patients (67 per cent). In 848 cases reported by Hudson and Chamberlain,[14] only 30.5 per cent of the children with acute appendicitis had had preceding attacks of abdominal pain. In our series the attacks of pain dated as far back as four years in 1 case and two years in 9. In the remainder pain had been first noticed from one to twelve months before. Most of these patients were old enough to describe their pain, and stated that it was cramplike and occurred in the umbilical region. The length of the attacks varied considerably with each patient. It is important to note that 32 patients (71 per cent) entered the hospital in acute attacks of pain as emergency cases, and that only 13 (29 per cent) entered for investigation of chronic abdominal pain.

TABLE 2. *Patients with* E. vermicularis *Infection of the Appendix but without Histological Evidence of Appendicitis.*

CLINICAL DATA	NO. OF CASES
Previous attacks of abdominal pain	30
No previous attacks of abdominal pain	15
Nausea and vomiting	25
Nausea but no vomiting	8
No nausea or vomiting	12
Tenderness and spasm in right lower quadrant	9
Tenderness but no spasm in right lower quadrant	28
No abdominal tenderness or spasm	8
Temperature (rectal):	
102–101°F.	7
101–100°F.	9
100– 99°F.	29
Leukocyte count:	
25,000–20,000	2
20,000–15,000	5
15,000–10,000	22
10,000– 5,000	14
None recorded	2

Nausea and vomiting were present in 25 cases (56 per cent) and nausea alone in 8 (18 per cent). The rectal temperature was below 100°F. in most cases, although 7 patients had temperatures of over 101°F. Physical examination revealed tenderness alone in the right lower quadrant in 28 cases (62 per cent), tenderness and spasm in 9 (20 per cent) and no abdominal tenderness or spasm in 8 (18 per cent). The leukocyte count was usually between 10,000 and 20,000. Search for eosinophilia was made in 16 cases; it was noted in only 1, in which the eosinophils were listed as 15 per cent.

A diagnosis of acute appendicitis was made and an immediate operation performed in 22* (69 per cent) of the 32 emergency cases. Elective appendectomy was performed in the others.

Pathological examination of the appendices of this group revealed no anatomic or inflammatory change attributable to *E. vermicularis*,[15] except in 3 cases where portions of pinworms were found in the submucosa. This finding has been reported frequently.[10]

*One patient had primary streptococcal peritonitis. The appendix was removed when the peritoneal cavity was drained, and the patient died. This was the only death in the group. Disease of the appendix was not the cause of the peritonitis.

Discussion

Cases of acute inflammation and pinworm infection of the appendix cannot be regarded as different in any particular from those of acute appendicitis without pinworm infection. In our series there was no clinical or pathological evidence justifying any other belief. However, various authors[1, 13, 16–19] believe that the parasites provide a mode of entry for pathogenic bacteria by burrowing into the wall of the appendix and thus initiate true acute appendicitis. It is known that such penetration does occur. This was true in 3 cases in the present series, but no inflammatory reaction was present.[15] Gordon,[10] after a careful pathological study of appendices infected with pinworms, concluded that the worms had migrated after the appendix had been removed, and found no inflammatory reaction in any case. The evidence, using histological studies as a standard, at present is equivocal as to whether or not pinworms initiate acute appendicitis.

The main problem, however, is presented by those patients who show the signs and symptoms of appendicitis and have pinworm infection of the appendix, yet give no histological evidence of appendicitis. Since in the vast majority of cases histological evidence of tissue reaction due to the parasite is absent, it is difficult to state how the worms cause symptoms. It has been suggested that the symptoms are due to penetration of the wall of the appendix by the worms,[20] or that the parasite causes a local toxic reaction in the appendix.[21] On several occasions we have seen the worms sticking into the submucosa when the appendix was opened immediately after removal. Despite the lack of knowledge concerning the mode of action of pinworms in the appendix, most authors[1, 2, 9, 12, 13, 18–23] think that the parasites must be responsible for the syndrome. The fact that patients who have complained of recurrent bouts of abdominal pain and who have pinworms in the appendix are relieved when the appendix is removed is strong evidence for this opinion. In our series a careful check-up of 29 of the 30 patients who had had recurrent abdominal pain and pinworms in the appendix revealed that in no case was there recurrent pain after appendectomy.

The clinical diagnosis of pinworm infection of the appendix cannot be made with certainty. It may be suggested by the picture given by Wood:[22] "The histories of my cases were long and inter-

mittent; vomiting was often absent, the temperature was usually normal or only slightly raised and the leukocytosis was slight." To this may be added a history of pinworm infection. Eosinophilia is of diagnostic value, but in our experience it was present in only 1 of the 16 cases in which it was looked for. A large number of patients, however, present a history and physical examination exactly like those of acute appendicitis, and there is no course except to treat them as cases of appendicitis. As a general rule it is not safe to attempt to treat with vermifuges patients who have appendiceal symptoms which may be caused by pinworms. In the first place, the diagnosis may be incorrect and the patient may have acute appendicitis; in the second place, the vermifuge may not act on the worms in the appendix.

Summary and Conclusions

Seventy-one of 1343 appendices removed at the Children's Hospital, Boston, from 1929 to 1939 were infected with pinworms.

Microscopical as well as gross inspection of the appendiceal contents is advocated in order to find the parasites.

Twenty-six patients had acute appendicitis and pinworm infection. The cases differed in no way from the usual picture of acute appendicitis in children.

Forty-five patients had no inflammatory change in the appendix but had pinworm infection. All had abdominal pain and all were relieved by appendectomy.

Twenty-nine of the 30 patients who had chronic abdominal pain were relieved by appendectomy.

Twenty-two patients who had no histological evidence of appendicitis but had pinworm infection of the appendix presented a syndrome exactly like that of acute appendicitis.

Pinworm infection of the appendix cannot be differentiated with certainty from acute appendicitis. It may be suggested by a history of pinworm infection and recurrent abdominal pain.

The mechanism of the mode of action of pinworms in the appendix is unknown.

The safest treatment of appendiceal symptoms due to pinworms is appendectomy.

References

1. Harris, W. H., and Browne, D. C.: Oxyuris vermicularis as a causative factor in appendicitis. J. A. M. A. **84**:650-654, 1925.
2. Brumpt, E.: *Précis de Parasitologie*. Fifth edition. Vol. 1, 1082 pp. Paris: Masson et Cie, 1936. Pp. 867-880.
3. Report of the Committee on Terminology. J. Parasitol. **23**:325-329, 1937.
4. Penso, G.: Il ciclo di sviluppo degli Ossiuri. Policlinico (sez. prat.) **42**:1943-1949, 1935.
5. Wright, W. H., and Bozicevich, J.: Studies on oxyuriasis. XI. Dermal and intradermal skin reactions in oxyuriasis. J. Parasitol. **23**:562, 1937.
6. Weller, T. H., and Sorenson, C. W.: unpublished data.
7. Cram, E. B.; Jones, M. F.; Reardon, L., and Noland, M. O.: The incidence of oxyuriasis in 1272 persons in Washington, D. C. Pub. Health Rep. **52**:1480-1504, 1937.
8. Cram, E. B., and Reardon, L.: Studies in oxyuriasis. XII. Epidemiological findings in Washington, D. C. Am. J. Hyg., Sect. D. **29**:17-24, 1939.
9. Beck, R. C.: Appendical oxyuriasis and appendicitis. Am. J. Surg. **25**:313-318, 1934.
10. Gordon, H.: Appendical oxyuriasis and appendicitis, based on study of 26,051 appendixes. Arch. Path. **16**:177-194, 1933.
11. Goodale, R. H.: Enterobius vermicularis of the appendix. New Eng. J. Med. **210**:372-374, 1934.
12. Warwick, M.: Relationship between oxyuriasis and appendicitis. Am. J. Clin. Path. **5**:238-248, 1935.
13. Andrä, K.: Appendicitis oxyurica. Arch. f. klin. Chir. **192**:618-630, 1938.
14. Hudson, H. W., Jr., and Chamberlain, J. W.: unpublished data.
15. Farber, S.: personal communication.
16. Rheindorf, A. J.: Wurmfortsatzentzündung ex oxyure. Med. Klin. **9**:53-57, 96-99, 133-136 and 177, 1913.
17. *Idem:* Ist die Oxyuris vermicularis imstande, aktio die Processuswand zu durchdringen, und ist sie ein blutsaugender Parasit? Centralbl. f. Bakt. **74**:604-617, 1914.
18. Cecil, R. L., and Bulkley, K.: On lesions produced in the appendix by *Oxyuris vermicularis* and *Trichocephalus trichiura*. J. Exper. Med. **15**:225-245, 1912.
19. Ney, G. C.: Pin worm appendicitis. Bull. Johns Hopkins Hosp. **23**:123-126, 1912.
20. Aschoff, L.: Appendicopathia oxyurica (pseudo-appendicitis ex oxyure). Med. Klin. **9**:249-251, 1913.
21. Schropl, E.: Skin tests with extract from oxyuris. Deutsche med. Wchnschr. **52**:1508, 1926.
22. Wood, W. A.: Appendicopathia oxyurica. M. J. Australia **1**:234, 1918.
23. Bell, M. A.: Oxyuris vermicularis and appendicitis. Arch. Pediat. **53**:649-653, 1936.

ROCKY MOUNTAIN SPOTTED FEVER

A Case Report

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ROCKY Mountain spotted fever is an acute disease rarely seen in this immediate area, although for several years it has occurred sporadically in the eastern states. It is fairly common in the District of Columbia and Maryland where the case here reported is presumed to have originated. The disease was originally described by Maxey[1] in 1899 in an article read before the Oregon State Medical Society, when he referred to it as spotted fever. In 1902 Wilson and Chowning[2] suggested the theory of transmission by ticks, and referred to the condition as spotted fever of the Rocky Mountains. In 1903 Anderson[3] referred to the condition as tick or spotted fever of the Rocky Mountains. Although especially common in the Rocky Mountain region and particularly in the Bitter Root Valley of Montana, it has of late been found in various communities throughout the United States and Canada. The work of Pinkerton and Hass[4] has established the relation between boutonneuse fever and the Eastern variety of spotted fever of our country.

This disease belongs to the typhus-like group of conditions due to rickettsial infections transmitted by ticks, mites, lice and fleas. The inoculation of the virus through the bite of an infected wood tick produces exanthematous tick fever, commonly called Rocky Mountain spotted fever. Man does not contribute to the perpetuation of the virus in nature as in the case of malaria or yellow fever. Instead the virus is propagated by infection of an animal host by the tick in the process of feeding, the animal then infecting other ticks; or through hereditary transmission by the female tick to her eggs. While a large percentage of cases undoubtedly occur as a result of a tick bite, infection may come about by contact with material from crushed, infected ticks. The importance of this is illustrated by the case reported herewith.

The animal hosts vary in different sections of the country. In New England they include chipmunks, woodchucks, rabbits and field mice. While dogs frequently carry ticks, it is not yet considered certain that they serve as a reservoir of the disease.

In 1906 Ricketts[5] began a study of Rocky Mountain spotted fever, and continued it until his death in 1910 from the rickettsial disease, typhus fever. He was able to infect Dermacentor ticks by feeding them on guinea pigs inoculated from a patient suffering with Rocky Mountain spotted fever. In 1931 *Dermacentor variabilis* was found to be the carrier of tick fever in the eastern United States.[6] This tick passes through larval, nymph and adult stages. In its more immature forms it feeds on mice, rabbits and chipmunks, thereupon dropping off the host for the purpose of molting. The adults frequently attach themselves to dogs. The tick usually climbs up on grass or shrubbery and fastens itself to a passing host, animal or human.

In 1916 Wolbach[7] made a search among infected ticks for the causative agent of Rocky Mountain spotted fever, and found a gram-negative Rickettsia in all tissues of infected ticks and in the vascular lesions of infected animals. This was subsequently confirmed by other investigators and the agent was called *Dermacentroxenus rickettsii*.

Before 1930 it was thought that this disease did not exist in the eastern United States, but in 1931 a number of cases were reported from this section.[6] Ticks have been found to be very prevalent on Cape Cod, Massachusetts, and several cases have occurred there in the last two years.[8] Summer residents often find ticks on themselves and on their dogs, and remove them. Occasionally the insects are found on bed linen left on the ground or hung so as to touch the grass or shrubs. The importance of protecting the hands when removing ticks, especially when the insect has been crushed, cannot be overestimated. Likewise, protection of the body, particularly the legs, when traveling through the grass or brush, and the examination of linen left out of doors should be made routine in sections where ticks are prevalent. The tick season in the eastern United States extends from the first warm days of spring to midsummer.

Recovery from Rocky Mountain spotted fever is believed to produce prolonged immunity although cases of re-infection have been reported. The mortality varies but is frequently high. For example, of 4 cases reported in New York in 1936, 2 were fatal, and of 4 cases reported in the District of Columbia in the same year, 2 were fatal.

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Case Report

A 35-year-old housewife was seen at home by one of us (N. A. W.) on June 20, 1938, with complaints of malaise, severe headache, generalized muscular aching and fever. The temperature was 103°F. Physical examination was negative except for tenderness over the region of the left kidney. Urinary examination showed a moderate number of pus cells, so that a probable diagnosis of pyelitis was made. The following day an irregular macular eruption appeared on the arms and scattered areas of the body. At that time it was learned that the patient had returned home on June 17 from a visit to Maryland near the District of Columbia border. While there, some time between June 5 and 12, she removed five ticks from a dog, some being crushed in the process. It is interesting to note that a short time previously the dog had been transported from Texas. The patient had no knowledge of any tick bite. The day after her return the patient began to complain of exhaustion and headache.

The rash became fairly widespread and involved the hands and feet. The temperature ran between 103 and 104.5°F. with no remission, and there was continuous severe headache. The patient gradually became lethargic, falling asleep even while being bathed. However, she could be easily roused. The skin became hypersensitive for a short time about a week after the onset of the rash, and a marked conjunctivitis with photophobia developed. The rash assumed a purplish-red appearance, and was particularly evident in areas of pressure such as those over the scapula regions, over the buttocks and on the dependent surfaces of the arms.

Figure 1. *Spotted Fever Rash on Arms.*

On June 22 the patient was examined by Dr. Fred Bailey, of the Boston Health Department, and Dr. Henry Pinkerton, of the Harvard Medical School. Inoculation of guinea pigs with specimens of blood taken at that time yielded results which were consistent with a diagnosis of spotted fever. Subsequent cross-immunity tests with a virulent spotted fever culture at the Department of Bacteriology, Harvard Medical School, demonstrated the existence of spotted-fever antibodies in the patient's serum.

The patient was admitted to the Carney Hospital on June 29, 1938, in essentially the lethargic state described above. On July 4 she began to show remissions in the fever, and on July 9 she was running a normal temperature, which continued until her discharge on July 19. The residual of the rash persisted for several months, and as late as October was easily visible on the legs when standing and on the arms on the application of a tourniquet.

During the height of the illness the pulse was between 120 and 130, although it had been practically normal in the early stages of the disease. The respirations were close to 40 for several days, although nothing to account for the increase was ever demonstrable in the lung fields. The white-blood-cell count was never high; at the onset it was only 10,000, and on admission it was 12,200, the highest count obtained. The red-cell count ran between 3,440,000 and 3,900,000, with a hemoglobin of 68 per cent. The polymorphonuclears averaged 88 per cent.

Treatment with an adequate blood concentration of sulfanilamide resulted in no improvement. The rest of the treatment was symptomatic and supportive.

This case is reported because of the rare occurrence of Rocky Mountain spotted fever in Massachusetts, and because its severe nature warrants

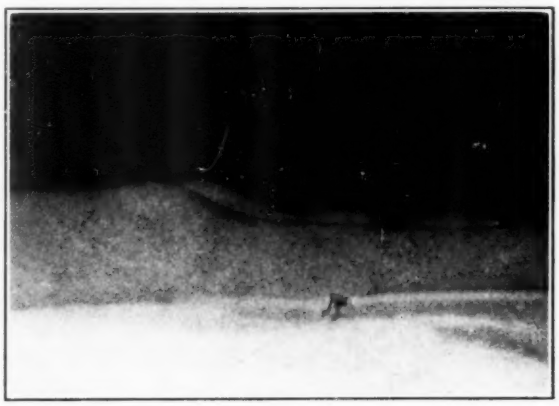

Figure 2. *Spotted Fever Rash on Legs.*

calling the attention of the medical profession to the possibilities of its prevention. Clinically the disease is indistinguishable from endemic typhus fever, but according to Pinkerton[9] the appearance of a rash on the soles and palms suggests it rather than typhus fever, in which such distribution is usually absent. The case also demonstrates the probability of infection without the actual bite of a tick. It suggests the advisability of prohibiting the interstate transportation of dogs during the tick season if it can be shown that such animals are reservoirs of rickettsial infection.

Summary

Rocky Mountain spotted fever is becoming commoner in the eastern states as a result either of local infection or of the entry of persons who have acquired the infection elsewhere. The case here reported showed the typical symptoms and signs of severe headache, conjunctivitis, high persistent temperature, elevated respirations with no demonstrable pulmonary cause, lethargy and characteristic embolic rash, with persistent evidence of the last for a long time after the subsidence of the infection. The progress of the case was not influenced by the use of sulfanilamide.

References

1. Maxey, E. E.: Some observations on the so-called spotted fever of Idaho. M. Sentinel **7**:433-438, 1899.
2. Wilson, L. B., and Chowning, W. M.: The so-called "spotted fever" of the Rocky Mountains: a preliminary report to the Montana State Board of Health. J. A. M. A. **39**:131-136, 1902.

3. Anderson, J. F.: Spotted fever (tick fever) of the Rocky Mountains: a new disease. Am. Med. **6**:506-508, 1903. Treasury Department, U. S. Marine Hospital Service, Hygiene Laboratory Bulletin No. 14. 50 pp. Washington: Government Printing Office, 1903.
4. Pinkerton, H., and Hass, G. M.: Spotted fever; experimental study of fièvre boutonneuse. J. Exper. Med. **64**:601-623, 1936.
5. Ricketts, H. T.: Demonstration of a micro-organism which apparently has a specific relationship to Rocky Mountain spotted fever. Tr. Chicago Path. Soc. **7**:254, 1909. Investigations concerning Rocky Mountain fever. Bull. Johns Hopkins Hosp. **20**:151, 1909.
6. Badger, L. F.; Dyer, R. E., and Rumreich, A.: Infection of Rocky Mountain spotted fever type; identification in eastern part of United States. Pub. Health Rep. **46**:463-470, 1931.
7. Wolbach, S. B.: The etiology of Rocky Mountain spotted fever. J. Med. Research N. S. **29**:121-126, 1916. The etiology of Rocky Mountain spotted fever: occurrence of the parasite in the tick. *Ibid.* N. S. **30**:147-150, 1916. The etiology and pathology of Rocky Mountain spotted fever; occurrence of parasite and pathology of disease in man; additional notes on parasite. *Ibid.* N. S. **32**:499-508, 1918.
8. McLaughlin, E. A., and Grover, M. L.: Rocky Mountain spotted fever in Rhode Island. Rhode Island M. J. **20**:139-143, 1937.
9. Pinkerton, H.: Criteria for the accurate classification of the rickettsial diseases (rickettsioses) and of their etiological agents. Parasitology **28**:172-189, 1936.

REPORT ON MEDICAL PROGRESS

VASCULAR DISEASES WITH PARTICULAR REFERENCE TO ARTERIAL HYPERTENSION*

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INVESTIGATORS in the field of physiology and the diseases of the peripheral vessels have been active in recent years. Progress in this field has been extensive.

METHODS

Stead and Kunkel,[1, 2] have devised a plethysmographic method for the quantitative measurement of the blood flow in the foot. The inherent error of this method is about 3 per cent. When the measurements are conducted at a temperature of 43°C., maximal dilatation of the vessels develops and therefore the maximal blood flow is measured. In 34 normal subjects the average blood flow was 17.1 cc. per minute per 100 cc. of tissue. The lowest value was 11.1 cc., and the highest 25.9 cc. The values were somewhat lower for men than for women. Comparative measurements indicated a considerably smaller reserve in the blood flow in the foot than in the hand. In the presence of arteriosclerosis and thrombo-angiitis obliterans the blood flow may be reduced to 50 per cent of normal before local symptoms or signs develop. When the blood flow reaches as low a level as about 5 cc. per minute per 100 cc. of tissue, or one third of normal, trophic disturbances are apt to appear. This method offers opportunity for a more precise study of a number of pertinent vascular problems.

Sodeman and Burch[3] have described a simple method which measures the distensibility of the skin with the aid of a small caliper of known calibration. In the presence of edema the distensibility decreases, and this is a factor in limiting the formation of edema. Changes in the distensibility have been found in a number of cutaneous diseases such as senile atrophy, allergic eczema and scleroderma.

Wright, Schneider and Ungerleider,[4] on the basis of questionnaires sent to medical schools, life-insurance companies and individual physicians, have pointed out the great variations existing in the technic of measuring arterial pressure. To remedy this they suggested an investigation of this problem by a national committee. This has actually been done recently.

Committees appointed by the American Heart Association and by the Cardiac Society of Great Britain and Ireland recommend the following procedure as the standard method for taking blood-pressure readings in man.[5]

Blood-Pressure Equipment. The blood-pressure equipment should be in good condition and calibrated at yearly intervals. Under these circumstances either mercurial or aneroid types of apparatus are capable of correct readings. The mercury manometer should be checked at intervals so as to be sure that the level of the mercury at rest is at the zero mark and that the air vent at the top of the glass tubing is not clogged. When readings are taken the apparatus must be on a flat surface at the level of the observer's eyes.

The Patient. The patient should be seated with the arms slightly flexed and the whole forearm supported at heart level. If readings are taken in any other position notation should be made. The patient should be allowed time (ten to fifteen minutes) to recover from any recent exercise or excitement. The time of day should be recorded.

Position and Method of Application of the Cuff. A standard-sized cuff 12 to 13 cm. in width should be used. The completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 3 cm. above the antecubital space and with the rubber bag applied over the inner aspect of the arm. Inflation should not cause bulging at the edges of the cuff. Special cuffs of suitable size should be used for the measurement of blood pressure in the leg or in children.

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Checking Palpatory and Auscultatory Levels. The pressure in the cuff should be quickly increased in steps of 10 mm. of mercury until the radial pulse disappears, and then allowed to fall rapidly. If the radial pulse returns at a higher level than that at which the first sound is heard, the palpatory reading should be accepted as the systolic pressure.

Application of Stethoscope. The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff. The lip of the stethoscope should make contact with the skin but with a minimum of pressure.

Determination of the Systolic Pressure. The cuff should be rapidly inflated to a pressure about 30 mm. above the systolic pressure and then deflated at a rate of 2 to 3 mm. of mercury per second. The level of the first sound should be considered the systolic pressure unless the palpatory level is higher. All unnecessary venous congestion should be avoided. It is well to take the blood pressure in both arms on the first examination. With premature beats the higher systolic pressure of the beats that terminate compensatory pauses should be ignored. With auricular fibrillation the average of a series of readings may be used.

Determination of the Diastolic Pressure and the Pulse Pressure. With continued deflation of the cuff, the point at which the sounds suddenly become dull should be known as the diastolic pressure. If this point differs from that at which the sounds disappear, it is recommended that both points be recorded, for example, 140 systolic, 80-70 diastolic. If these two levels are identical the blood pressure should be recorded, for example, 140 systolic, 70-70 diastolic.

Montgomery and Starr[6] have described the use of four simple apparatus in the treatment of vascular diseases. These are a foot cradle provided with a thermoregulator for the maintenance of heat over the lower extremities, a simple instrument for the administration of iontophoresis, a specially constructed bed for the comfort of patients with vascular diseases of the lower extremities and a small suction apparatus devised for the fingers.

ARTERIAL HYPERTENSION

So far as the etiology of hypertension is concerned, more evidence has been brought to light on the importance of renal ischemia in several types of hypertension.[7] Rytand[8] has demonstrated, with the aid of ingenious animal experiments, that renal ischemia is responsible for the hypertension of coarctation of the aorta. Weiss and Parker[9] in a systematic study of the natural history of pyelonephritis have investigated the relation of the disease to arterial hypertension. They claim that the inflammatory reactions of the tissues are responsible for the development of hyperplastic arteriolosclerosis not only in the active but also in the healed cases of pyelonephritis. A relation was found between renal vascular changes and arterial hypertension. The hypertension associated with chronic pyelonephritis can be malignant in type. It has been estimated that pyelonephritis is responsible for 15 to 20 per cent of the total number of cases of malignant hypertension of varied origin. Weiss and Parker call attention to the fact that pyelonephritis, particularly in its chronic stage, should be considered as one type of Bright's disease.

Wiggers[10] has reviewed the present knowledge on the dynamics of the circulation. He points out the similarity between the hemodynamics and the vascular states of certain types of experimental and human hypertension. He believes that renal hypertension in man is caused by humoral and not by nervous factors. The most important resistance in hypertension is located in the arterioles and in the prearterioles, but Wiggers enumerates evidence indicating that changes are present also in the larger arteries. Decreased elasticity of the aorta and other arteries is responsible in part for the high pulse pressure and marked elevation of the systolic pressure.

Tigerstedt and Bergman[11] demonstrated in 1898 the existence of a vasopressor substance in the kidney, called renin. Recent interest[12, 13] in the renal causation of hypertension has redirected attention to the specific role of this substance. It is too early to claim, however, that renin is the humoral agent responsible for the renal type of arterial hypertension. Hessel[14] reports a detailed study on the action of renin. He observed that following the daily injection of renin for a period of five weeks or over, elevation of the arterial pressure persisted as long as seven months. It is particularly significant that he was able to demonstrate the presence of this substance in the venous blood of the kidney. Prinzmetal, Friedman and Abramson[15] found more pressor effect after the injection of saline extracts of ischemic kidneys than after injection of a similarly prepared extract of the normal contralateral kidney. A number of additional reports of less importance have been published on the presence and action of renin in different species of animals. It is of interest that transfusion of the blood of patients with malignant hypertension failed to produce elevation of the arterial pressure in normal subjects.[16]

In the evaluation of therapeutic measures in hypertension, lack of information on the natural history of the condition is a handicap. It is for this reason that the contribution of Hines[17] is significant. He reports on the level of the arterial pressure of 1185 persons from ten to twenty years after the initial reading. The majority of patients with elevated pressure at the first measurement had developed increasing pressure, while only a relatively small percentage of those with normal readings at the start showed hypertension.

So far as the vascular lesions are concerned, it

has been demonstrated again that various types of arteriolar and arterial lesions are apt to be present in a number of organs in the presence of hypertension.[18–20]

In the chemotherapy of hypertension no significant advances have been made. The therapeutic value of various types of sympathetic surgery is still unsettled, notwithstanding optimistic reports. Craig[21] claims that 70 per cent of the cases have been benefited by subdiaphragmatic section of the splanchnic nerve. This is in agreement with the results obtained by Freyberg and Peet,[22] who claim that in approximately 60 per cent of their cases the blood pressure was lowered, at least for several months. Moore[23] sectioned the splanchnic nerve in 22 patients. A lowering in the blood pressure was maintained for over a year in 45 per cent of the cases. Before a final answer can be given on the specificity of surgical operation certain types of control studies are essential. From such a point of view the observations of Volini and Flaxman[24] are of interest. These investigators, impressed by their belief that the majority of proposed therapeutic measures rapidly pass into obscurity, undertook a comparative evaluation of the results of nonspecific surgical measures (hysterectomy, cholecystectomy and prostatectomy) and of specific neurological operations, such as extensive sympathectomy, splanchnic nerve resection and celiac ganglionectomy. They followed the effects of operations on 52 hypertensive patients. Twenty-seven of these were suitable for analysis. Reduction of blood pressure following the nonspecific operations was common. Symptomatic improvement was a usual feature in the group. Regardless of the type of operation, all patients were relieved of symptoms such as headache, nervousness, dizziness, fatigue, insomnia and palpitation for four months to nine years. These authors assert that the results obtained by specific operations can be duplicated by non-specific surgical measures.

Partial constriction of one renal artery in animals results in marked and sustained hypertension. If the kidney, corresponding to the constricted artery, is excised such hypertension is abolished. The physiologic principle involved in these experiments has a distinct therapeutic applicability. Cases of unilateral renal ischemia associated with arteriosclerosis or congenital hypoplasia of the renal artery, and those with unilateral inflammatory kidney disease, are quite frequent. Reports[25–27] on successful abolition of arterial hypertension following surgical removal of such unilaterally diseased kidneys are appearing in increasing numbers. This surgical procedure is a rational one, but the follow-up period of the cases operated is too short to warrant a final expression of opinion.

In animals with constricted renal arteries efforts have recently been made to improve the renal circulation and reduce the hypertension through experimentally induced collateral circulation. This procedure has not been applied to the treatment of human hypertension, although a clinical report[28] on the beneficial effects of omentonephropexy has appeared.

ARTERIOSCLEROSIS

The etiology of arteriosclerosis is still an unsettled problem. In a systematic investigation Winternitz, Thomas and LeCompte[29] have emphasized the concept that hemorrhage within the vascular wall represents a significant source for the development of lipoid deposits and subsequently atheromatous plaques. They discuss in detail considerable indirect evidence in favor of this assumption. They present a method for the demonstration of the vascular network in the intima of vessels of animals and of man. Leary[30] has also reported on the vascularization of atherosclerotic lesions. The normal intima is not vascularized, and vascularization develops only as a part of the repair process. In his experience internal hemorrhages play no etiologic role, because they represent late phenomena. Cholesterol is carried to the site of vascular deposition in macrophages, the presence of the latter not being due to local vascular hemorrhages.

In a group of 100 diabetic patients Kramer[31] found the incidence of arteriosclerosis to be 38 per cent. Roentgen-ray studies of the extremities revealed calcified vessels in 63 per cent of the cases of arteriosclerosis. It is of interest that only 21 per cent of the arteriosclerotic group showed elevated lipid content of the blood. The simple histamine test was found to be useful in the estimation of the degree of collateral circulation. Stroud and Shumway[32] found that in a group of 57 patients with coronary occlusion 7 had suffered from intermittent claudication, while in a group of 106 patients without heart disease only 1 was so affected. Patients with hypertension are more apt to complain of cramps at night than are normal persons.

RAYNAUD'S DISEASE

In the light of recent investigations this condition is considered a special type of sclerosis of the small arteries of the digits. Lewis[33] has studied the disease diligently and has recently reported again on his experiences. A comparative study of the arterial lesions of the fingers revealed that in patients with quite severe spasm the intimal thick-

ening, though pronounced, was no greater than that in subjects who suffered no symptoms. It is assumed that in such patients the muscular layer is overactive in response to certain types of stimuli. In cases with intermittent attacks associated with unhealed necrosis, thrombosis of the arteries was frequent. Lewis considers Raynaud's disease a manifestation of an occlusive structural disease, and not the result of an overactive vasomotor system. Preganglionic sympathectomy in 6 cases failed to abolish the local abnormality.[34] The initial temporary postoperative vasodilatation disappeared within as short a time as one week.

THROMBO-ANGIITIS OBLITERANS

An extensive statistical analysis of 948 cases with thrombo-angiitis obliterans has been presented by Horton.[35] It is of interest that twenty-eight nationalities were represented, and only 28 per cent of the patients were Jews. As high as 98 per cent were men. Ninety-three per cent consumed tobacco. The mean age of the men was 41.8 years and of the women 38.8 years. In a study of the causation of death in a group of 175 patients, 47 were shown to have died as a result of coronary heart disease, 12 of cerebral hemorrhage, 12 of gangrene or following amputation and 7 of fatal pulmonary embolism. A significant study on the cerebral manifestations of thrombo-angiitis obliterans is presented by Hausner and Allen.[36] In a group of 500 patients with peripheral vascular involvement, 11 patients with clinical evidence of cerebral vascular involvement were observed. Usually the cerebral symptoms appeared after the manifestation of difficulties in the extremities, but in 3 patients cerebral symptoms preceded peripheral vascular insufficiency. The commonest manifestation of cerebral involvement was transient or permanent hemiplegia. Transient confusion, aphasia, disorientation and loss of memory were also present. Hemianopia was present in 2 patients.

The role of smoking in thrombo-angiitis obliterans is still unsettled. Westcott and Wright[37] deny that patients with thrombo-angiitis obliterans show a higher incidence of positive cutaneous reactions than do those in the control group. Harkavy,[38] on the other hand, claims that 70 per cent of the patients exhibit increased sensitivity. A study of serum calcium, serum protein, blood urea, serum lecithin, serum phosphorus, blood fatty acids and blood cholesterol failed to reveal significant changes in a study of 105 patients by Roth, Maclay and Allen.[39]

REFERENCES

1. Stead, E. A., Jr., and Kunkel, P.: A plethysmographic method for the quantitative measurement of the blood flow in the foot. J. Clin. Investigation **17**:711-714, 1938.
2. Kunkel, P., and Stead, E. A., Jr.: Blood flow and vasomotor reactions in the foot in health, in arteriosclerosis, and in thrombo-angiitis obliterans. J. Clin. Investigation **17**:715-723, 1938.
3. Sodeman, W. A., and Burch, G. E.: A direct method for the estimation of skin distensibility with its application to the study of vascular states. J. Clin. Investigation **17**:785-793, 1938.
4. Wright, I. S.; Schneider, R. F., and Ungerleider, H. E.: Factors of error in blood pressure readings; a survey of methods of teaching and interpretation. Am. Heart J. **16**:469-476, 1938.
5. Standardization of blood pressure readings. Joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland. Am. Heart J. **18**:95-101, 1939.
6. Montgomery, H., and Starr, I.: Four physiotherapeutic devices for treatment of peripheral vascular disorders. Am. J. Med. Sc. **197**:485-493, 1939.
7. Scott, R. W.: Hypertension a century after Bright. J. A. M. A. **111**:2460-2463, 1938.
8. Rytand, D. A.: The renal factor in arterial hypertension with coarctation of the aorta. J. Clin. Investigation **17**:391-399, 1938.
9. Weiss, S., and Parker, F., Jr.: Pyelonephritis: its relation to vascular lesions and to arterial hypertension. Medicine **18**:221-315, 1939.
10. Wiggers, C. J.: The dynamics of hypertension. Am. Heart J. **16**:515-543, 1938.
11. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf. Skandinav. Arch. f. Physiol. **8**:223-271, 1898.
12. Landis, E. M.; Montgomery, H., and Sparkman, D.: The effects of pressor drugs and of saline kidney extracts on blood pressure and skin temperature. J. Clin. Investigation **17**:189-206, 1938.
13. Merrill, A.; Williams, R. H., and Harrison, T. R.: The effects of a pressor substance obtained from the kidneys on the renal circulation of rats and dogs. Am. J. Med. Sc. **196**:240-246, 1938.
14. Hessel, G.: Ueber Renin. Klin. Wchnschr. **17**:843-849, 1938.
15. Prinzmetal, M.; Friedman, B., and Abramson, D. I.: The nature of arterial hypertension with special reference to the role of the kidney. Ann. Int. Med. **12**:1604-1616, 1939.
16. Friedman, B., and Prinzmetal, M.: Vasomotor effects of blood in patients with hypertension and animals with experimental hypertension. Ann. Int. Med. **12**:1617-1631, 1939.
17. Hines, E. A.: The prognostic significance of hyperreactibility of the blood pressure in normal subjects. J. A. M. A. **112**:1016, 1939.
18. Odel, H. M.: Arteriolar changes in the myocardium in diffuse arteriolar disease with hypertension, Group IV. Proc. Staff Meet. Mayo Clin. **14**:210-214, 1939.
19. Morlock, C. G.: Arterioles of the pancreas, liver, gastro-intestinal tract and spleen in hypertension. Proc. Staff Meet. Mayo Clin. **14**:214-217, 1939.
20. Rosenberg, E. F.: The brain in malignant hypertension. Proc. Staff Meet. Mayo Clin. **14**:217-222, 1939.
21. Craig, W. McK.: Essential hypertension: the selection of cases and results obtained by subdiaphragmatic extensive sympathectomy. Surgery **4**:502-509, 1938.
22. Freyberg, R. H., and Peet, M. M.: The effect on the kidney of bilateral splanchnicectomy in patients with hypertension. J. Clin. Investigation **16**:49-65, 1937.
23. Moore, C. H.: Surgical treatment of hypertension. South. Surgeon **7**:353-357, 1938.
24. Volini, I. F., and Flaxman, N.: The effect of nonspecific operations on essential hypertension. J. A. M. A. **112**:2126-2128, 1939.
25. Butler, A. M.: Chronic pyelonephritis and arterial hypertension. J. Clin. Investigation **16**:889-897, 1937.
26. Leadbetter, W. F., and Burkland, C. E.: Hypertension in unilateral renal disease. J. Urol. **39**:611-626, 1938.
27. Barney, J. D., and Suby, H. I.: Unilateral renal disease with arterial hypertension; report of a case apparently cured following nephrectomy. New Eng. J. Med. **220**:744-746, 1939.
28. Abrami, P.; Iselin, M., and Wallich, R.: Essai de traitement de l'hypertension artérielle d'origine rénale par la revascularisation chirurgicale du rein (néphro-omentopexie). Presse méd. **47**:137-139, 1939.
29. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: *The Biology of Arteriosclerosis*. 142 pp. Springfield, Ill.: Charles C Thomas, 1938.
30. Leary, T.: Vascularization of atherosclerotic lesions. Am. Heart J. **16**:549-554, 1938.
31. Kramer, L. I.: Various methods of determining the early diagnosis of arteriosclerosis in diabetes. New Eng. J. Med. **220**:278-282, 1939.
32. Stroud, W. D., and Shumway, N. P.: Intermittent claudication as early symptom of cardiovascular disease. Pennsylvania M. J. **41**:894-897, 1938.
33. Lewis, T.: The pathological changes in the arteries supplying the fingers in warm-handed people and in cases of so-called Raynaud's disease. Clin. Sc. **3**:287-319, 1938.
34. *Idem:* Raynaud's disease and preganglionic sympathectomy. Clin. Sc. **3**:320-336, 1938.
35. Horton, B. T.: The outlook in thrombo-angiitis obliterans. J. A. M. A. **111**:2184-2189, 1938.
36. Hausner, E., and Allen, E. V.: Cerebrovascular complications in thromboangiitis obliterans. Ann. Int. Med. **12**:845-852, 1938.
37. Westcott, F. H., and Wright, I. S.: Tobacco allergy and thromboangiitis obliterans. J. Allergy **9**:555-564, 1938.
38. Harkavy, J.: Hypersensitiveness to tobacco and biopsy studies of skin reactions in vascular disease. J. Allergy **9**:475-488, 1938.
39. Roth, G. M.; Maclay, E. V., and Allen, E. V.: Blood in thromboangiitis obliterans. Arch. Int. Med. **62**:413-422, 1938.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 25501

PRESENTATION OF CASE

First Admission. A fifty-five-year-old lawyer was admitted to the hospital complaining of periodic epigastric distress.

About twenty years before admission the patient began to experience brief periods of epigastric distress, relieved by the ingestion of a soft, bland diet. A detailed history of the attacks could not be obtained, but there was no vomiting, rare nausea and no melena, and his bowels were normal. Twelve years before entry, following a six-week sojourn in France where he ate freely, he had had an attack of diarrhea, with black stools and slight gastric distress. By the time he received a medical examination his stools were free of blood; his symptoms responded promptly to treatment. Since that time he had had spells of nausea, vomiting and gastric distress lasting a few days to a few weeks. These were always preceded by periods of business strain; he characteristically reacted "first emotionally, then gastrointestinally." Each attack cleared with ample sedation and a bland diet, which was rapidly increased both in amount and in types of food. Six years before entry a duodenal ulcer was demonstrated roentgenologically, and an outside gastric analysis showed a free acid of 25 units, a total acid of 40 units and no blood. Four years before admission a two-hour diet with alkaline powders brought relief to attacks of upper abdominal "gnawing pain" which recurred every two hours. These attacks usually occurred in the spring and fall and were supposedly never precipitated by dietary carelessness. The symptoms increased progressively, however, until eight months before entry when he developed severe, persistent vomiting, with epigastric pain which proved intractable to treatment. He vomited everything including atropine, and progressed into an unquestioned temporary psychosis, as shown by excitement and disorientation as to time, place and people. From this he emerged fairly quickly and was placed on a bland diet. One month later he was eating practically everything and was well except for slight residual weakness. He had a similar attack a few days before admission.

Physical examination revealed a well-developed and nourished man. The heart, lungs and abdomen were normal. The blood pressure was 130 systolic, 80 diastolic.

The temperature, pulse and respirations were normal.

The examination of the urine showed a specific gravity ranging from 1.010 to 1.014 and the slightest possible trace of albumin. The sediment had 3 white blood cells, a rare red blood cell and numerous bacteria per high-power field. The blood nonprotein nitrogen was 58 mg. per 100 cc., and the blood chlorides 522 mg. Roentgenograms of the gall bladder by the Graham technic failed to show any evidence of stones. A gastrointestinal series showed that the stomach was unusually high and flexed on itself. The gastric rugae were rather prominent, and there was considerable spasm of the median portions of the stomach and of the pylorus. Peristalsis was irregular and at times quite active. There was a constant and characteristic clover-leaf deformity of the duodenal bulb. The evidence of active spasm and hyperperistalsis was greater than that at an observation ten months previously.

The temperature, pulse and respirations remained normal throughout his hospital stay of nineteen days. During this time he received Sippy powders, with a supplementary dietary regimen, sedation, occasional parenteral fluids and bed rest; he was discharged improved.

Second Admission (two years later). The patient was readmitted complaining of vomiting and epigastric pain. He stated that for many months he had been increasingly annoyed with postprandial gaseous abdominal distention, "bloating" and "belching." With the bloating, which usually occurred about fifteen minutes after eating, he developed severe mid-epigastric pain relieved only by purposefully vomiting the ingested food. These emeses happened from one to twelve times a day and were usually spontaneous, but he added that there were periods of a month or more when these complaints were absent. He also stated that he had been slightly dyspneic on moderate exertion and that his ankles had been questionably swollen on occasions. He had noted slight nocturia. The physical examination was unchanged from the first admission. Urinary examination showed an amber cloudy urine with a neutral reaction and a specific gravity of 1.009 on two occasions; there was the slightest possible trace of albumin and occasional red and white blood cells. The blood showed a red-cell count of 3,800,000 with 65 per cent hemoglobin, and a white-cell count of 8700; the smear was normal. The vomitus was guaiac negative. A urinary concentration test showed specific gravities ranging from 1.005 to 1.009 and

1570 cc. excreted in twenty-four hours. Phenolsulfonephthalein kidney-function tests revealed a 22 per cent excretion at the end of two hours, with 6 per cent during the first fifteen minutes. The blood nonprotein nitrogen ranged from 92 to 78 mg. per 100 cc. The serum protein was 6.9 gm. per 100 cc., and the chlorides were equivalent to 100 cc. of N/10 sodium chloride; the serum uric acid was 3.6 mg. per 100 cc., the serum calcium 11.66 mg., the serum phosphorus 6.24 mg., and the carbon-dioxide combining power 65 and 48 vol. per cent. X-ray films of the chest were negative. A gastrointestinal series showed a small pocket in the esophagus which filled with barium, located near the aortic arch. Gastric peristalsis was more vigorous than normal. There was some delay in the passage of barium from the stomach to the duodenum, and the latter showed a constant deformity of much the same character as that previously noted. However, spot films of the duodenal bulb showed no evidence of an ulcer crater. Intravenous pyelograms revealed kidney outlines which were about half normal size. The dye was secreted very slowly so that at no time were the kidney pelves or ureters sufficiently well filled to show their outlines distinctly, but they were apparently negative.

The patient's temperature, pulse and respirations were normal. He was treated in much the same way as at the time of his previous entry, and was discharged on the twenty-ninth hospital day.

Third Admission (six months later). He was readmitted complaining of great pain and tenderness over the flexor tendons of the right wrist joint. Pressure over these tendons caused excruciating pain, but movements of the hand without motion of these tendons caused no pain. He had first noted the difficulty on awakening in the middle of the night with his hand over his head; sudden flexion of the wrist had produced an excruciating pain which kept him awake day and night, in spite of rather heavy medication. It was further noted that the patient had experienced definite pain in the legs with exercise and that the pulsations in the right popliteal and posterior tibial arteries were faint, that of the dorsalis pedis artery almost impalpable. The laboratory and x-ray data were unchanged. The wrist and hand were splinted, and a plaster mould and gauntlet made; the patient was discharged home where the pain in his hand improved rapidly.

Fourth Admission (six months later). He was again readmitted because of several vomiting attacks following fatigue of physical or emotional origin. He had done "fairly well" since his last discharge until several days of vomiting had followed the upsets associated with the installation of a telephone. He was dehydrated, oliguric and distended and had an acetone breath. He was given parenteral fluids. The serum nonprotein nitrogens successively were 98, 62 and 80 mg. per 100 cc., and the serum chlorides were equivalent to 92, 96 and 100 cc. of N/10 sodium chloride. After slight improvement he was discharged on the sixth hospital day.

Fifth Admission (two and a half years later). This admission resulted from an acute upper respiratory infection of two days' duration, associated with an intense desire to urinate, and incontinence. He dribbled 60 to 90 cc. of urine every one and a half hours. Examination showed a fairly marked coarse tremor of the hands, feet and tongue. There were dyspnea and orthopnea, and the chest was barrel shaped. The heart seemed to be slightly enlarged to the left and downward, the sounds were distant and of rather poor quality, the blood pressure was 160 systolic, 92 diastolic, and the pulse 112. The breath was definitely uriniferous. The prostate was slightly enlarged, round, solid and suspiciously hard on the right. The urine had a specific gravity of 1.004 and a + albumin; the sediment showed a rare red and 4 white blood cells per high-power field. He was discharged relieved on the sixth hospital day.

Final Admission (six months later). Six years after the first recorded entry, the patient returned to the hospital. For one month prior to admission he had suffered with attacks of substernal pain, which were relieved with nitroglycerin and codeine. Twenty-four hours before entry the discomfort became severe and was unrelieved by medication. He also had experienced nausea, vomiting, belching and cough without sputum. His condition became critical; the blood pressure fell to 95 systolic, 60 diastolic. He quickly failed and died a few hours after hospitalization. An electrocardiogram taken before death showed a ventricular rate of 110, an inverted T_1, a sagging ST_2, an inverted T_4 and an upright T_3, with normal rhythm and moderate left-axis deviation.

Differential Diagnosis

Dr. Alfred Kranes: I think we can be reasonably certain that when this patient first began to be ill he had a duodenal ulcer and that this accounted for his symptoms during the early part of his illness. That is borne out by the later x-ray evidence — although no crater was ever demonstrated — and also by the story that twelve years before entry he had had an attack of bleeding presumably from the ulcer, although we have

no objective evidence that he did bleed. The story then continues to record gastrointestinal symptoms, but they seem to change a bit in character. He began to have nausea, vomiting and gastric distress, lasting two days to a week. The implication is that they were on an emotional basis, — which they may very well have been, — but in view of what subsequently follows we have to take them more seriously and wonder if any new development had taken place which had changed his original gastrointestinal symptoms. Concerning the gastric analysis showing a free acid of 25 units, it would be important to know whether that was the height of the curve or whether it was a fasting specimen. If he had a free acid of only 25 units after alcohol and histamine, it would be some evidence that there was impairment of gastric function. It would be unusual, although it does occur with duodenal ulcer, to have so little hydrochloric acid present, and it makes you wonder whether there was something else which was depressing gastric secretion. Then he developed severe persistent vomiting attacks, during which he experienced a temporary psychosis and which recurred and led to his first hospital admission. At that time we have the first observations pointing toward renal insufficiency. He had an elevated nonprotein nitrogen and a fixed specific gravity of his urine. X-ray study revealed a duodenal deformity without any evidence of an active crater. May we see the films, Dr. Schatzki?

Dr. Richard Schatzki: The films show that he definitely had an old duodenal ulcer as far back as eight years preceding death. There was a clover-leaf deformity of the cap, apparently with an active ulcer at that time. In 1938 the last film also shows the clover-leaf deformity of the cap and evidence of activity. This is the film taken in 1935; it shows a scar, but no evidence of activity.

Dr. Kranes: As I said, he showed evidence at that time of renal insufficiency. One might reasonably wonder, however, whether he had any structural changes in the kidney or whether the signs of renal insufficiency were the result of persistent vomiting or of administration of alkali. It is well known that people with peptic ulcers may develop uremia following vomiting, so-called achloremic uremia, and also as a result of the prolonged or intensive administration of alkalies. We are not told how much alkali he received.

Dr. Chester M. Jones: He received tremendous amounts during the first portion of his treatment. He received none after 1935, when I first saw him. He had been treated for four years on routine ulcer medication with a great deal of alkali.

Dr. Kranes: We can reasonably ask here then whether the administration of alkali may have depressed the renal function so that he went into uremia. Such cases have been reported. The exact mechanism is not quite clear, but it certainly occurs. It would have been of extreme interest at that time to have known the carbon-dioxide combining power. I think we can infer that the uremia was probably not due to vomiting, because the blood chlorides, although somewhat depressed, were not down in the range where achloremic uremia takes place (300 mg. per 100 cc.). This transient psychosis may have been due to uremia. People with uremia do have psychoses. On the other hand it may have been a drug psychosis, the result of hypodermic medication in a vomiting patient with poor renal function and therefore faulty excretion of the drug. His improvement under Sippy powders, during his first admission, argues very much against alkalies as the cause of his renal insufficiency. If it was, he should have become worse. It begins to appear that his vomiting was probably uremic and not due to his ulcer, since he did not have pyloric obstruction by x-ray study and the type of vomiting described is not that of pyloric obstruction. If this is true, alkaline therapy seems to have played no part in the renal picture, since the vomiting improved with the administration of Sippy powders.

There are several significant omissions in this record despite its length. I do not want to appear ungrateful for all this information, but nevertheless in a patient with renal disease one is interested in certain specific things. The blood pressure is one, and there is scant mention of it throughout this long record. Anemia is another, and there is only one red count, and one hemoglobin, recorded during the second admission; furthermore, no examination of the fundi is recorded at any time.

Dr. Jones: In 1935, examination of the fundi showed the vessels small in caliber, but was otherwise not important. The blood pressure at that time was 130 systolic, 80 diastolic.

Dr. Kranes: On the second admission the blood pressure is not recorded. He continued to show signs of marked renal failure by all tests. There are some interesting blood chemical findings during this admission which are unusual in uncomplicated uremia. Three things strike me. The first is a uric acid of 3.6 mg. per 100 cc., which is normal. With the marked nitrogen retention which this patient showed one would expect a much higher uric acid in the blood; I do not know why it should have been normal, and cannot explain it. The second is the carbon-dioxide combining power, which was normal or slightly

above normal, whereas most patients with uremia develop an acidosis with a consequent lowering of the carbon-dioxide combining power. There are two possible explanations for this normal or slightly elevated reading: he may have been receiving large amounts of alkali, which would tend to keep it up, or he may have been vomiting quite a lot of chloride, which would have the same effect. However, if the latter were the case one would expect the blood chlorides to be low. Since they are reported to be normal, the administration of alkali probably explains the normal level. The third point is the serum calcium of 11.6 mg. per 100 cc. This in a healthy person might be considered normal or perhaps at the upper limit of normal. However, in a patient with renal failure it is definitely abnormal, particularly with a serum phosphorus of 6.24 mg. per 100 cc. Uremic patients usually have a low blood calcium, about 6 to 9 mg. as a rule, whereas this is quite above what one would expect. It makes one wonder about two possibilities. Could this patient with prolonged renal insufficiency have developed secondary parathyroid hyperplasia? Although there is no other proof that the parathyroid glands were involved, it is the most probable explanation. Could this patient possibly have had a "myeloma" kidney? Elevated serum calciums are not uncommon in cases of multiple myeloma, with or without renal insufficiency. However there is not the slightest evidence of this.

What the acute process in the right wrist was, I do not know. There is no examination recorded of the wrist, and I have no idea what it was. It reminds me of one patient that was studied here extensively several years ago, a patient with prolonged renal insufficiency, who developed metastatic areas of calcification near various joints and tendons which were quite painful. That patient also had a marked secondary hyperparathyroidism as a result of renal failure, and it is quite conceivable that this acute wrist represents some such phenomenon — metastatic calcification in a tendon. Six months later he was again admitted with another episode of renal failure, and improved.

Finally six months before his last admission we have the first evidence that there may have been something wrong with the prostate, although nothing more is said about it and we are left high and dry as to whether the prostate was enlarged or whether there was any real evidence of cancer. I shall disregard it, since nothing further is said about it. One would also like to know what happened to the dribbling or incontinence, whether it was a temporary affair or lasted any length of time. I am inclined to believe it was temporary because no further mention is made of it. On this admission we have the first recorded evidence that his blood pressure had become elevated — 160 systolic, 92 diastolic. Previous to that it had apparently been normal. He finally was admitted with an episode which I take to be fairly characteristic of coronary thrombosis and which proved fatal.

So far as the gastrointestinal lesion goes, I think he probably had a healed duodenal ulcer, active many years before but healing during the latter part of his life, possibly the result of the lowered chloride secretion that occurs in the stomachs of patients who develop uremia. At any rate, I do not believe it played much of a role in his death or in the major part of his illness. He must have had something else going on in the gastrointestinal tract, probably in the nature of a uremic gastritis. Are there any more films that might help?

DR. SCHATZKI: The films show no evidence of gastritis. That does not exclude the presence of gastritis.

DR. KRANES: Patients with uremia often develop gastrointestinal lesions, anywhere from the mouth to the anus. They excrete urea in the gastrointestinal tract and ammonia forms, producing severe irritation of the mucous membrane.

So far as the renal situation goes, I am inclined to believe that this patient had some structural changes in the kidneys. There are several things that stand out in the renal story; the first is the duration. We know he had been in renal failure for eight years, and probably longer. The second is the essentially normal urine, except for the fixed specific gravity — no albumin and a negative sediment. The absence of hypertension, except toward the end, is another significant and unusual finding. Just what type of renal disease this patient had, I am sure I do not know. There is nothing in this story or in the past history that gives us any clue as to the type of renal disease that was going on. On a purely statistical basis I think chronic glomerulonephritis would probably be the most likely diagnosis. Another possibility is a chronic pyelonephritis or a healed pyelonephritis. There is no evidence from the history of either one, but both are possible. I think we also have to keep in mind the possibility that this man had "myeloma" kidneys, but of this there is no evidence. Are there any x-ray films of the bones?

DR. SCHATZKI: In regard to the "myeloma" kidney, he had kidneys that were definitely smaller than is normal for a man of his size. They are, at most, half the size they ought to be. At that time he had very poor concentration.

DR. KRANES: With kidneys as small as that one can fairly safely exclude myeloma. I think the safest thing to say is that this patient had nephritis. I shall leave it up to Dr. Mallory to tell us whether it was chronic glomerulonephritis,

pyelonephritis or possibly some other type which we have not mentioned. Whether his prostate played any role, I do not know, but I rather think not. There is not much evidence of chronic prostatism in this patient. I should also guess that he had a fairly good degree of parathyroid hyperplasia and that the terminal illness was most likely coronary thrombosis.

Dr. Jones: This story is a long one, and even at its present length it did not include certain things that are of interest but do not affect the diagnosis so far as Dr. Kranes is concerned. It represents the life history of several diseases. I saw this man in 1935 at the request of Dr. John Taylor, who had followed him as a duodenal-ulcer patient for several years. Up to that time the diagnoses had been ulcer and psychoneurosis. He was one of the most mercurial individuals I have ever seen. Under any pressure or disturbance he developed gastrointestinal symptoms. He did not tolerate alkalies very well, and in 1935 he showed for the first time the picture of alkalosis. On one occasion a few months later, while being given calcium carbonate, which ordinarily does not produce much trouble, he developed an alkalosis which was mild in degree but definite so far as the blood chemistry was concerned. The calcium carbonate was eliminated and he had no further trouble from the point of view of this renal disturbance. The first study of the urine was in 1931, four years before I first saw him, and this showed a concentration of 1.028, with no albumin. In 1931 he had no obvious evidence of nephritis. From 1932 on the specific gravity never went higher than 1.016. In 1935 the first studies that I was able to do on him showed that he had a specific gravity ranging from 1.010 to 1.014. His output was 1465 cc. during the day, and 1570 cc. at night. The quantity of night urine was increased over the day urine for the four years before death. From then on, and even at that time, he showed all the chemical findings one could desire of renal insufficiency, and a breath which was strongly uremic. It was not uriniferous. It was the breath of one with nitrogen retention. I remember that one morning I called Dr. Walter Bauer into the office to make a diagnosis. He smelled this man's breath and said: "He has nephritis and is in uremia." That persisted for five years. The blood creatinin was 5.6 mg. per 100 cc., which is high. Ordinarily one expects to find the patient seriously ill with as high a creatinin as that. The urinary picture was marked, as he went along, with increasing frequency and nocturia. At no time did he have any evidence of inability to handle himself. He was a fairly normal person up to within a few weeks of death. He was ambulatory and went to California six weeks before death, and aside from some unpleasant attacks of circulatory disturbance on the trip, he got along perfectly well. In 1936 he began to complain of very slight substernal oppression on exertion. One year before death he complained because he was unable to swim a quarter of a mile. He carried out vigorous exercise before death. Until six months before death he was able to swim 100 yards in fairly cold water with only a little subsequent substernal oppression. At the end of 1938 he had definite attacks of intermittent claudication in both legs. He could walk only so far and then had to stop for a while; but it did not prevent his going. He just stopped and rested. The pain in the wrist was diagnosed as tenosynovitis. It is possible he had some calcium in the tendon sheath at that time. In the last year of his life he had symptoms of rather characteristic repeated anginal attacks, finally leading to an absolutely characteristic attack of coronary thrombosis. He walked into the office and said: "I have something serious the matter with my heart." He died thirty-six hours later.

Clinical Diagnoses

Coronary infarction.
Chronic nephritis, with arteriosclerosis.
Duodenal ulcer.

Dr. Kranes's Diagnoses

Duodenal ulcer, healed.
Chronic nephritis:
  Glomerulonephritis?
  Pyelonephritis?
Parathyroid hyperplasia.
Coronary thrombosis.

Anatomical Diagnoses

Duodenal and pyloric ulcer, slightly active.
Healed pyelonephritis.
Parathyroid hyperplasia.
Coronary sclerosis, with thrombosis.
Calcification of annulus fibrosus of mitral valve, early.

Pathological Discussion

Dr. Tracy B. Mallory: As you gathered from the clinical story this is a most unusual case, and I do not believe I can do as well with the pathology as the clinicians have done. I can confirm all that they have said. The final cause of death was coronary thrombosis. We found nearly all

the coronary vessels occluded, some chronically and some acutely. The kidneys were extremely small, weighing only 100 gm. There was a very marked secondary hyperplasia of the parathyroid glands, and there was a duodenal ulcer which spread across the pyloric ring, slightly into the stomach, showing at least some degree of activity. There are, however, a great many things that are more difficult to explain. First, is the question of what type of kidney disease we have here. We often get a good deal of help from the gross appearance of the kidneys. I should say we got none in this case because the kidneys had a great many of the retention cysts that one sees in elderly people, and the gross shape of the kidneys was so distorted by the cysts that it was impossible to make out what it might have been. Microscopically, they showed a disproportionately high destruction of tubules, a relative maintenance of glomeruli and a considerable degree of lymphocytic infiltration, perhaps a little more than the average chronic nephritis would show. There are one or two tubules that contain a few leukocytes, but certainly nowhere is there abscess formation or anything that could be considered active pyelonephritis. The tubules contained an unusually large number of casts. On the whole, the findings are those that are usually considered characteristic of a chronic or burnt-out pyelonephritis. We have recently had our attention called to that condition as a frequent cause for what seems clinically to be essential hypertension. It is interesting to note that this man had so little evidence of hypertension, even at the very end. With the prolonged renal insufficiency, virtually amounting to six years of uremia, it was inevitable that the parathyroid glands would be enlarged. We did not actually weigh them, but from the measurements we can assume about 2 gm. of parathyroid tissue, which is a tenfold increase above the normal. On the other hand, every case we have seen heretofore with marked secondary hyperplasia of the parathyroid glands has shown evident osteitis fibrosa on microscopic examination even if it was not evident by x-ray during life.

A Physician: Did the diet have anything to do with it?

Dr. Mallory: It seems possible, and I have no other explanation to offer.

There was a final anatomical finding which I cannot explain — an area of what seemed to be caseous necrosis in the myocardium high up in the ventricular wall and just underneath the mitral ring, which was partially calcified. It was fairly circumscribed, measuring about 2.5 by 1.0 cm. From time to time we see cases with a very marked calcification of the annulus fibrosus of the mitral ring, both with and without evidence of valvular involvement. This man showed a completely calcified vegetation on the mitral valve, as well as partial calcification of the myocardial focus. Whether it represents an early stage of the syndrome of calcification of the annulus fibrosus, I do not know, and I have no idea what name to give it. It may, of course, have been merely a focus of metastatic calcification such as occurs so often in the syndrome of renal rickets, but the absence of any other focus of calcification makes this seem improbable.

CASE 25502

Presentation of Case

A seventy-year-old, Italian-born, American laborer was admitted to the hospital complaining of epigastric pain.

The patient was well until ten months before admission when he began having four-hour attacks of epigastric pain which "came and went," usually accentuated by heavy meals. The pain was dull but at times was severe enough to prevent him from eating. Occasionally there was associated nausea, but no vomiting. He was seen in the Out Patient Department nine months before entry, where gastrointestinal x-ray studies showed a normal esophagus, stomach and duodenum. He was placed on a normal diet with a tablespoonful of mineral oil daily, and was discharged with no definitely established diagnosis. Eight months before admission he was again seen in the Out Patient Department and stated that he was improved. Six months before entry, however, the patient's family noticed that he was losing weight. Apparently his appetite had been poor because of a subjective fear of producing epigastric distress with eating. Three months before admission he began having almost weekly attacks of fever, each lasting one or two days. With one of these episodes six weeks before entry he was seen by an outside physician, who referred the patient to another hospital where he remained about four weeks. While there he was studied for the still persisting, recurrent epigastric pain. A few days later he became jaundiced, but gradually the pain disappeared and he felt no further steady discomfort. The jaundice waxed and waned as the stools became increasingly pale. He suffered two shaking chills during this period of hospitalization, but for some undetermined reason he was discharged home where he remained until his admission to this institution. Two days before entry he developed severe shaking chills with almost white stools and deepening jaundice; he felt poorly, was anorexic and had another attack of chills and fever on the day of admission. He had lost

a great deal of weight during the present illness. The past, family and marital histories were not contributory.

Physical examination revealed an emaciated, deeply jaundiced, feverish man, who had a severe shaking chill during the examination. The skin was hot and dry, and both skin and sclerae were icteric. The oral and pharyngeal mucous membranes were dry, and the throat was covered with a thick tenacious exudate. The heart was enlarged 1.5 cm. beyond the midclavicular line in the fifth interspace. There was a soft blowing apical systolic murmur; the rate was 110, with regular rhythm. The blood pressure was 136 systolic, 80 diastolic, and there was "moderate peripheral arteriosclerosis." The lungs showed dullness at the right base, with subcrepitant inspiratory rales in the right axilla. The abdomen was flat, with voluntary spasm in the upper quadrant but no tenderness. A small palpable mass in the right upper quadrant was found to descend below the costal margin on deep inspiration and was thought by the examiner to have been the gall bladder. The left lobe of the liver was enlarged and filled the upper half of the epigastrium. There were no other positive findings.

The temperature was 103°F., the pulse 110, and the respirations 30.

The urine examination showed a + bile test, and there were 2 to 4 white blood cells per high-power field in the sediment. The blood showed a red-cell count of 3,100,000 with 70 per cent hemoglobin (Tallqvist), and a white-cell count of 17,000; the red cells were microcytic and hypochromic. The hematocrit was 31.5 per cent, and the plasma prothrombin 40.9 per cent normal; a bromsulfalein test showed 100 per cent retention; the van den Bergh was 20 mg. bilirubin direct, the hippuric acid 1.7 gm. and the plasma cevitamic acid 0.44 mg. per 100 cc. The blood serum cholesterol was 89 mg., the nonprotein nitrogen 20 mg., and the serum protein 5.7 gm. per 100 cc.; the serum chlorides were equivalent to 101.9 cc. of N/10 sodium chloride, and the carbon-dioxide combining power to 19 cc. of N/10 carbonic acid.

X-ray studies of the chest revealed a normal-sized heart, a tortuous and calcified aorta and increased lung markings. There was no definite evidence of metastases or pneumonia. Films of the pelvis and lumbar spine showed moderate hypertrophic changes, with marked osteoporosis but no evidence of metastases.

The patient ran a short, downhill course with spiking temperature (97 to 103°F.), rapid pulse (100 to 130) and rapid respirations (20 to 40). On the third day his white-blood-cell count was 21,600 with 94 per cent polymorphonuclears. The dehydration was difficult to combat. He became irrational and stuporous and developed ankle edema. A large, tender liver was palpated, but there was no evidence of ascites. Dullness with decreased breath sounds was noted at the right base. He failed rapidly and died on the fifth hospital day.

Differential Diagnosis

Dr. Richard H. Sweet: The report of the x-ray studies seem to indicate that the films were negative. Is there any comment to make about them? No mention is made of a Graham test.

Dr. Richard Schatzki: Examination of the upper gastrointestinal tract nine months before admission showed a normal stomach and duodenum, with the exception of a small diverticulum in the region of the papilla of Vater. The next examination is a flat abdominal film taken at the time of admission. It shows some osteoporosis but not more than one would expect in a patient of his age. There are arteriosclerotic and degenerative changes but nothing that would help with the diagnosis. This is a calcified mesenteric node. There is no special flat film of the gall-bladder region. The only film is one taken with the patient face up, and in it I cannot see any stones in the region of the gall bladder. The other film is one of the chest, apparently taken at that admission; as the patient was lying down, it is not a six-foot film, probably four or five feet, and I refrain from making a statement regarding the size of the heart. The lung markings are increased, as if he might have been slightly decompensated. The lung markings are, however, not very definite.

Dr. Sweet: We get little information of value from the x-ray studies, except negative evidence. It is obvious after reviewing this case that we are dealing with a history starting rather vaguely and ending up with a definite case of so-called "Charcot's intermittent hepatic fever," which we know is usually superimposed on some type of biliary-tract obstruction. Whether such obstruction is due to stone, stricture or carcinoma is not always possible to say. Of course in our clinical experience the number of cases with stone in the duct is greater than that of those with carcinoma, so we are apt to have the impression that with this syndrome we should consider carcinoma only rarely. When I started to think about the case that was my first impression, but I am not sure that it is correct. Therefore, let us try by a careful analysis of the symptoms and findings to decide on what basis this case of intermittent hepatic fever rests.

First of all this patient with a life-long history of apparently good health, began at the age of seventy to suffer pain, which is one of the most important symptoms to analyze in any case history. I get the impression, however, that it was never a severe lancinating type of pain such as one often hears about in cases with stone. It is described as dull, accentuated by meals and located in the epigastrium; it apparently did not radiate, and once or twice it is referred to as "distress." There is very little mention of it in the history. Could it have been due to stone or to carcinoma? We think of those with carcinoma as not having pain. That is usually true with carcinoma of the pancreas, but with carcinoma in the ducts, pain of this type may very well occur. On the other hand, one need not have severe pain in cases with stone, and in fact such patients often complain only of distress and a vague feeling of discomfort. Occasionally there is a stone in the ducts without any pain.

The jaundice began later — eight months after onset. It is said to have fluctuated, but that is apt to be an unreliable observation. It certainly tended to be progressive and became very severe, judging from the way the history is worded. We know that a sizable percentage of cases with stone in the common duct may occur without jaundice — Dr. Daniel F. Jones used to put it at about 40 per cent of all cases; but we also know that in cases in which the obstruction is due to progressive stricture, caused either by pancreatitis or by malignant disease, jaundice, while it may later be intermittent and allow some bile to go through into the stools, tends to be progressive and to become severe. So from the type and nature of the jaundice in this case one guesses that it was due to carcinoma rather than to stone.

Nausea is not mentioned as a prominent symptom, and I have the impression from my observation of patients that gallstones do not ordinarily produce much nausea. I should expect, however, that if the patient had carcinoma of the pancreas or some such condition there would have been more nausea. When the liver is invaded with carcinoma, it is often a predominant symptom. The anorexia might go with either condition, but it is described here as being due to fear of pain, in other words, fear to eat because he might have pain as a result. Later, with the jaundice and the evidence of liver obstruction and enlargement, anorexia might very well have been due to liver damage. The fever and chills, occurring in attacks with remissions and coming after the jaundice had become manifest, represent a good clinical description of the Charcot syndrome. So if we were to confine our analysis to a review of the history, I think we should have to say that the obstruction might be due to stone or to carcinoma. I have somehow the impression that it is due to both.

So far as the physical examination goes, we note first of all that there was marked emaciation, which was an early sign. That may have been due to anorexia or fear of eating, but it was severe and progressive and it may well have meant that he had malignant disease rather than stone. We must remember that this patient was well, we assume, until he reached the age of seventy, and then over the course of ten months he steadily lost weight. He had constant anorexia and repeated attacks of pain, and later, fever and chills. In other words, the disease was progressive. My impression is that if it had been entirely due to stone there would have been periods when he was relatively well, although I admit that he could have died of a stone that obstructed the common duct, with superimposed infection in the biliary tract. The jaundice we have talked about. The stools eventually became acholic, and stayed so. The usual signs of fever, dry skin and so forth were obvious and need not enter into the discussion. The dullness and rales in the chest suggest that he might have had pneumonia. This was not borne out by x-ray study, and that is a common experience.

We then come to the questionable mass in the region of the gall bladder. I should assume from the description that the gall bladder was felt; on the other hand it is described as small. We are accustomed, as you know, to feeling a large, distended gall bladder in cases with obstruction of the common bile duct due to carcinoma of the pancreas, according to Courvoisier's law. But that need not be so, and although I do not believe he had carcinoma of the pancreas we need not rule it out on that basis or rule it in either. The gall bladder was felt, however. The other important physical finding was the asymmetrical enlargement of the liver. The record mentions an enlarged left lobe, but nothing is said of the right; this suggests to me that there was some malignant process in the liver itself during the end of his illness.

One can sum up the laboratory findings by saying that they tell us chiefly that he had anemia, obstructive jaundice, diminished liver function and acidosis. We have commented on the x-ray studies. The course in the hospital is obvious and to be expected.

What did this patient have? We know that he had infection of the biliary tract, but what was the underlying lesion? I have covered in the discussion most of the essential points. The physical

examination toward the end of his life suggests to me that he had at that time a carcinoma of the liver. The knowledge that carcinoma of the liver is exceedingly rare as a primary disease and more often dependent on disease in the duct system of the liver or gall bladder or some adjacent viscus and the matter also of the questionably palpable gall bladder which was not particularly large, all enter into the consideration of the diagnosis. I suggest that this man had carcinoma of the biliary system, invading the liver, perhaps originating in the gall bladder and, therefore, perhaps in a gall bladder that contained stones, because we know that carcinoma of the gall bladder is commonly associated with gallstones. We also know that gallstones are quite common without the occurrence of carcinoma. To sum up, I believe there was infection of the liver and obstruction of the common duct. I cannot say for sure whether the obstruction was due to stone or carcinoma, but I think he had malignant disease, as I have described, and possibly stones as well. His long life without any symptoms is certainly against stones, in spite of the fact that we have all seen patients with stones who have gone through life without any symptoms.

Clinical Diagnoses

Carcinoma of head of pancreas, with obstructive jaundice.
Pneumonia, right lower lobe.

Dr. Sweet's Diagnoses

Carcinoma of gall bladder, with invasion of the bile ducts and liver.
Cholelithiasis?

Anatomical Diagnoses

Carcinoma of gall bladder, with invasion of liver and colon and obstruction of bile ducts and portal vein.
Cholecystocolic fistula.
Splenomegaly.
Icterus.
Ectopic pancreas, surrounding duodenum.

Pathological Discussion

Dr. Tracy B. Mallory: The autopsy showed carcinoma, and I think Dr. Sweet was right in placing the primary source in the gall bladder. It forms the only apparent exception, that I can remember in our series here, to the rule that carcinoma of the gall bladder is always associated with demonstrable gallstones. We could not find a gallstone, but there was a good reason for it because he had a fistula between the gall bladder and the colon, a rather wide one through which, without question, even a large gallstone could pass and probably had passed into the colon. The tumor had invaded widely into the bed of the gall bladder and throughout the right lobe of the liver. There were only two nodules in the left lobe. The liver was not strikingly enlarged, and I think what was felt and interpreted as the left lobe was the spleen, which was big, weighing about 500 gm. Enlargement of the spleen is quite unusual in cases of primary carcinoma of the biliary-duct system. The explanation for it in this case appeared to be that the tumor had grown down into the gastrohepatic ligament, had completely destroyed and obliterated both hepatic ducts and had grown about the portal vein to such an extent that it is reasonably certain it was causing a significant degree of obstruction.

One anatomic finding was a little unusual. The second portion of the duodenum was almost completely encircled by an ectopic pancreas. It was normal pancreatic tissue, however, not tumor, and I doubt if it played any part in his symptomatology.

Dr. Grantley W. Taylor: Could the long-standing fever and apparent Charcot's syndrome have been due to infection?

Dr. Mallory: In some of the sections of the liver there were focal abscesses, and whether the fever should be explained on the basis of sepsis which had spread through the cholecystocolic fistula or was truly of the Charcot type due to extensive carcinoma within the liver, I cannot say. Certainly both were present.

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THE PLATFORM OF THE AMERICAN MEDICAL ASSOCIATION

The Board of Trustees of the American Medical Association has recently formulated a set of proposals, — a so-called "Platform of the American Medical Association," — which embodies in a reasonable and practical way many of the suggestions and recommendations relative to the problems concerning the health and medical care of the people of the United States which have been made by the House of Delegates in the past several years. Although this cannot strictly be termed "the platform" until officially adopted at the next session of the House of Delegates, it so closely conforms to the proposals sponsored by the latter that little doubt can be entertained as to its eventual acceptance.

The platform is as follows:

1. The establishment of an agency of the federal government under which shall be co-ordinated and administered all medical and health functions of the federal government exclusive of those of the Army and Navy.

2. The allotment of such funds as the Congress may make available to any state in actual need, for the prevention of disease, the promotion of health and the care of the sick on proof of such need.

3. The principle that the care of the public health and the provision of medical service to the sick is primarily a local responsibility.

4. The development of a mechanism for meeting the needs of expansion of preventive medical services with local determination of needs and local control of administration.

5. The extension of medical care for the indigent and the medically indigent with local determination of needs and local control of administration.

6. In the extension of medical services to all the people, the utmost utilization of qualified medical and hospital facilities already established.

7. The continued development of the private practice of medicine, subject to such changes as may be necessary to maintain the quality of medical services and to increase their availability.

8. Expansion of public health and medical services consistent with the American system of democracy.

The several points brought out in the platform refer to nothing that is new, but they do serve to express, in succinct form, the principles which have been, and still are, advocated by the Association. Furthermore, they represent constructive suggestions, with no hint of the attitude of destructive criticism for which the Association has been censured in the last two years.

The platform advocates a single federal agency for medical and health functions. It approves the granting of federal funds to the states for promoting such functions, provided there is proof of need. It emphasizes that the expansion of preventive medicine and the provision of care for the indigent and medically indigent are local problems and that existing qualified medical and hospital facilities should be considered in any proposed extension of service. It recognizes the need for increased avail-

ability of medical services, but warns that the private practice of medicine should continue, that the present quality of medical care should be maintained and that any expansion should be consistent with the American system of democracy.

Whether the solons in Washington will attempt to revise pending legislation in such a way as to conform to the principles set forth in this platform remains to be seen. The recommendations advanced at the National Health Conference in 1938 and the proposed Wagner Bill indicate that the governmental authorities have preconceived, though possibly alterable, ideas in regard to the requirements of proper health legislation. If this be true, there is all the more need for bringing this practical, though somewhat belated, platform to the attention of those individuals in Washington who are responsible for the drafting and enacting of laws relative to the health and medical care of the people of the United States.

PSYCHOSOMATIC MEDICINE

In recent years there has been a growth of interest in psychosomatic medical problems and research is going forward in this line of endeavor. It is not surprising, therefore, that a special journal, *Psychosomatic Medicine*, has been started to publish papers on the psychological aspects of medicine, as well as on experimental studies of various types. It is to be published quarterly, under the sponsorship of the Committee on Problems of Neurotic Behavior, Division of Anthropology and Psychology, National Research Council, Washington, District of Columbia. The first number was issued in January, 1939, and contains a statement of the aims of the editors, which is to "encourage and bring together studies contributing to the understanding of the organism as a whole." Recent studies of emotional factors in the etiology and the course of organic illness have demonstrated that the scientific method is as essential to satisfactory management of patients with psychoses as it is to that of individuals showing somatic aspects of dysfunction. The first issue of the journal considers some of these problems. Three papers are given over to a discussion of the functions of the hypothalamus, and there follows a symposium of seven papers devoted to the subject of hypertension. *Psychosomatic Medicine* is a valuable addition to the field, and if the first number can be used as a guide, one expects that the journal will be of value to the medical profession.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

PUERPERAL INFECTION FOLLOWING NORMAL DELIVERY

Mrs. L. T., a thirty-four-year-old woman, was admitted to the hospital on September 30, 1927, complaining of fluctuating fever,—which was highest in the evening,—backache, and pain and tenderness in the lower abdomen. On September 7, 1927, the patient's eleventh child had been delivered uneventfully at home. On the second postpartum day she experienced a sudden, severe headache and a chill. Her temperature while at home had varied from 99 to 103°F. She had remained in bed and had received symptomatic treatment from the attending physician. During this time she had had considerable hypogastric tenderness on deep pressure; the lochia had been serosanguineous for two weeks, then it had changed to a thick yellowish discharge of moderate amount.

The family history was non-contributory. The patient had had the usual children's diseases. In 1913 the patient had had an "abscessed tube" following childbirth, and in 1926 a cholecystectomy. She had had one miscarriage. Catamenia began at twelve, were regular with a twenty-eight-day cycle and lasted three to four days with no pain.

On examination at entry the patient seemed to be in fairly good condition. She was rational and felt quite comfortable. The temperature was 103°F., the pulse 96, and the respirations 20. Her head and neck were essentially negative; the thorax, heart and lungs were also normal. The abdomen was soft and flabby, with marked tenderness throughout the hypogastrium. There was an operative scar in the right upper quadrant. The extremities showed moderate varicosities and nor-

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

mal reflexes. The blood showed a white-cell count of 9600 and a hemoglobin of 55 per cent. The urine contained many pus cells. A diagnosis of puerperal sepsis was made.

The treatment of the slight cough and abdominal pain was largely symptomatic. The patient received Creolin douches twice a day, with ice to the lower abdomen intermittently. Progress was essentially uneventful. Throughout her hospital stay her backache remained practically constant. She had a persistent dry cough and varying amounts of pelvic pain. Her temperature was of the picket-fence, septic type.

On October 10, vaginal examination disclosed a subinvoluted, retroverted uterus with old cervical lacerations. No masses were found, and the tenderness was moderate. On October 23 a pelvic examination showed some induration at the base of the left broad ligament, but no definite masses. By November 6 a palpable mass had developed in the left lower quadrant.

The patient's temperature during the first four days ranged from 100 to 103°F. During the next eleven days it remained between 100 and 102°F., coming down to normal for the following three days. For the next five weeks the temperature fluctuated between 98 and 103.6°F., finally reaching normal on November 14, with a slight rise on November 18 when the patient got out of bed. From then on the chart was normal, and she was discharged on November 23, recovered.

A blood culture taken on October 24 showed *Staphylococcus albus*. The white-cell count varied between 9000 and 12,000, the red-cell count remained at about 3,500,000, and the hemoglobin ranged between 55 and 65 per cent. The urine continued to show many pus cells.

Comment. This case represents the characteristic course of puerperal infection resulting in parametric involvement. The onset, accompanied by a chill, occurred within thirty-six hours of a normal delivery. The treatment was entirely conservative. There is no note as to a vaginal examination at the time of entry, and in the absence of definite signs of pelvic involvement by masses or induration, the use of any kind of douche is open to question. On the other hand when there is definite evidence of pelvic involvement, copious hot douches given under low pressure are considered of value.

Blood examination revealed a moderate anemia. In cases of sepsis with accompanying anemia small transfusions are very often valuable. The positive blood culture of *Staphylococcus albus* showed that treatment should be entirely conservative. No known treatment has any specific effect on this organism, and the growth may well have been due to contamination. Puerperal infection, like most infections, will usually subside if treated symptomatically and conservatively.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions of the Medical Postgraduate Extension Courses have been arranged for the week beginning December 18:

BRISTOL NORTH

Thursday, December 21, at 4:00 p.m., at the Morton Hospital, Taunton. Gonorrhea in the Female. Instructor: Alonzo K. Paine. Lester E. Butler, *Chairman.*

ESSEX SOUTH

Tuesday, December 19, at 4:00 p.m., in the Conference Room of the Salem Hospital, Salem. Head and Spine Injuries. Instructor: Donald Monro. J. Robert Shaughnessy, *Chairman.*

MIDDLESEX EAST

Tuesday, December 19, at 4:00 p.m., at the Melrose Hospital, Melrose. Complications in Obstetrics: Illustrated by case histories. Instructor: James C. Janney. Walter H. Flanders, *Chairman.*

WORCESTER (Milford Section)

Tuesday, December 19, at 8:30 p.m., in the Nurses' Home of the Milford Hospital, Milford. Pneumonia. Instructor: Donald S. King. Joseph Ashkins, *Chairman.*

WORCESTER NORTH

Friday, December 22, at 4:30 p.m., in the Nurses' Home of the Burbank Hospital, Fitchburg. The Use of Drugs in the Treatment of Childhood Infections. Instructor: James M. Baty. George P. Keaveny, *Chairman.*

ANNUAL PRIZE FOR INTERNS

The attention of interns in Massachusetts hospitals is called to the fact that a prize of $50.00 has been offered by the Massachusetts Medical Society for the best written and most comprehensive case report submitted by one of their number holding an internship in any Massachusetts hospital which is approved by the American Medical Association for intern training during 1938-1940.

This report is to be typewritten, and when completed is to be sealed, unsigned, in a plain envelope, which in turn is to be placed together with a separate slip bearing the name and address of the contestant, in a larger envelope, and sent to: Committee on Medical Education and Medical Diplomas, Massachusetts Medical Society, 8 Fenway, Boston.

The contest this year closes May 5, 1940. Reports may be submitted at any time prior to that date.

DEATHS

BURKE — JAMES J. BURKE, M.D., of Easthampton, died November 16. He was in his eightieth year.

Born in Chicopee, he attended the Holy Name School and Holy Cross College. He received his degree from Bellevue Hospital Medical College in 1885.

He was a member of the Massachusetts Medical Society and the American Medical Association.

Dr. Burke married Mary A. Powers who died in 1930. There were no children.

DAMSKY — Charles Damsky, M.D., of Lynn, died December 3. He was in his forty-sixth year.

Dr. Damsky received his degree from the Middlesex College of Medicine and Surgery in 1921, and studied in Austria, Italy and England. He had practiced in Lynn for fifteen years, and was chief orthopedic surgeon at the Lynn Hospital.

He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow, two sons, a brother and six sisters survive him.

HUGHES — Frank Hughes, M.D., of Dorchester, died September 13. He was in his sixty-eighth year.

Dr. Hughes was born in Sussex, England. He received his degree from Tufts College Medical School in 1910. He held memberships in the Massachusetts Medical Society and the American Medical Association.

His widow and a daughter survive him.

MISCELLANY

NOTES

Harvard University has recently announced the promotion at Harvard Medical School of Dr. C. Guy Lane to clinical professor of dermatology and that of Dr. Francis R. Dieuaide to associate professor of medicine.

The trustees of Middlesex University have recently announced the appointment of Dr. John Hall Smith as dean of the School of Medicine. Dr. William M. Konikov, who has been serving both as dean and as professor of anatomy, found that the duties of both positions made too great a demand upon his time and resigned as dean in order to devote his full energies in a teaching capacity.

Dr. Smith received his medical degree from the Louisville Medical College in 1896 and has practiced surgery in Boston since 1898. He is a member of the Massachusetts Medical Society and a fellow of the American Medical Association. He has been actively engaged in medical education for over twenty-five years and retired from practice some ten years ago to devote his entire time to the administrative affairs of Middlesex University. At the time of his appointment as dean, Dr. Smith was professor emeritus of anatomy and of clinical surgery on the medical faculty. He designed and supervised the construction of the new group of medical buildings on the university campus, and the erection of this medical group was made largely possible through substantial funds donated by Dr. Smith over a period of years.

The trustees have appointed Dr. David L. Davidson, professor of biochemistry, as assistant to the dean.

CORRESPONDENCE

PASSER OF BAD CHECKS

To the Editor: Dr. Herbert C. Kimberlin, of Trenton, Missouri, has requested the co-operation of this department in warning oculists against a man who is passing bad checks. The checks are drawn to an amount exceeding the cost of the glasses, and the difference is received in cash from the oculist. Working north and east from Missouri, the man was last heard of in New York State.

His description is given in the following letter written to Dr. C. M. Sneed, of Columbia, Missouri. Unfortunately, the check-passer reached Dr. Sneed before the letter did, costing Dr. Sneed $15.00.

I am writing you regarding a man who is running around the country buying glasses, especially from oculists, and usually giving a check to the amount of $30.00. This man tries to simulate a farmer, and he usually has a notation on the check to him for corn, a cow, hogs and so forth. The name on the check to him is no doubt forged, and there is no doubt that his endorsement on the back of the check is forged. The man is about five feet ten inches tall, weighs about 155 pounds, has light sandy hair and blue eyes and is smooth shaven, with a ruddy complexion, and about forty-nine years old.

Should a man come into your office making an attempt to cash a check as described above, unless proved to be absolutely authentic, please notify Sheriff of Grundy County, Trenton, Missouri.

He usually signs his name on the back of the check in a very rough, but plainly legible, hand and signs it W. C. Curran; he usually wishes the difference between the amount of the check and the price of the glasses in cash, but does not call for the glasses. Should he sign his name and such a check be presented to you, please have the sheriff intercept him.

Should you have any information regarding a man of his description passing checks of the above description, please inform the sheriff above named, Dr. R. C. Pearson, Maryville, Missouri, or myself.

We have further information to the effect that the wanted man has passed checks bearing the name of J. B. Powers, W. C. Cursey and J. C. Gardner. He was using the latter name at the time he was in Olean, New York.

Paul J. Jakmauh, M.D.,
Commissioner of Public Health.

State House,
Boston.

HARVEY CUSHING AND BOOKS

To the Editor: Dr. Harvey Cushing loved books. He wrote once: "Books are the most important tools of our craft." He loved to read them. We were told recently in a resolution relative to his death that "books and journals flowed freely and, at times, almost weekly" from the Boston Medical Library to the hospital where he worked, carried away in armfuls by the "faithful Gus."

Dr. Cushing loved not only to read books, but also to own them. He was a great collector of Americana. And his library, so rich in early American medical works, medical incunabula and so forth, was always open to the research worker and the bibliophile. In that connection, I should like to relate — and it is the purpose of this letter — an incident which might be of interest for the light it throws upon the personality of Dr. Cushing.

A few years ago, after receiving a catalogue from a certain bookdealer, I sent an order for a rather rare item, — Schoepff's *The Climate and Diseases of America,* — only to find out that Dr. Cushing had been an earlier bird and had gotten the worm. To my surprise, a few days later I received the book from Dr. Cushing, with a note telling me that he was sorry to have been ahead of me in the purchase of the book and that he was sending it to me for my own perusal. I was a complete stranger to him and yet he was sending me that precious little volume before having had a chance to read it himself!

John Shaw Billings did the same thing once for Osler, lending him a rare book. And Osler left it on the train from Washington to Baltimore, and it was never recovered.

How many collectors would have done what Cushing did? I know I would not.

GABRIEL NADEAU.

Rutland State Sanatorium,
Rutland, Massachusetts.

RESULTS OF JULY BOARD EXAMINATIONS

To the Editor: I am enclosing a statement of the results of the July, 1939, examination conducted by the Board of Registration in Medicine.

STEPHEN RUSHMORE, M.D., *Secretary.*

State House, Boston.

NOTICES

REMOVAL

SAMUEL ORLOV, M.D., announces the removal of his office to 341 Main Street, Wareham.

JEWISH MEMORIAL HOSPITAL

The next staff meeting of the Jewish Memorial Hospital will be held in the hospital auditorium, 45 Townsend Street, Roxbury, on Wednesday evening, December 20, at 8:30. Dr. Richard Ohler will speak on the subject, "Hypertension." A collation will be served.

The medical profession is invited to attend.

School	First Time		Second or Third Times		Fourth or More Times		Total		Total Applicants
	Passed	Failed	Passed	Failed	Passed	Failed	Passed	Failed	
Middlesex University	12	17	3	21	3	22	18	60	78
Tufts College Medical School*	11						11	0	11
Ghent*			1				1	0	1
Kansas City University of Physicians and Surgeons		2		10		7	0	19	19
College of Physicians and Surgeons (Boston)	1	1		8		7	1	16	17
Mid-West College of Medicine (Kansas City)		1	1	5		1	1	7	8
Massachusetts College of Osteopathy†		9		5	2	2	2	16	18
Kirksville College of Osteopathy†		3		2		3	0	8	8
Philadelphia College of Osteopathy†	1	6		1			1	7	8
Edinburgh*	1			1			1	1	2
Lausanne*				2			0	2	2
Prague*		2					0	2	2
Des Moines Still College of Osteopathy†			1				1	0	1
Woman's Medical College of Philadelphia*	1			1			1	1	2
Vienna*	3	2					3	2	5
Northwestern University Medical School*	1						1	0	1
Berlin*	2	1					2	1	3
University of Rochester School of Medicine*	2						2	0	2
Boston University School of Medicine*	1	1					1	1	2
University of Iowa College of Medicine*	1						1	0	1
Freiburg*	1	1					1	1	2
University of Pittsburgh School of Medicine*	1						1	0	1
Georgetown University School of Medicine*	2	1					2	1	3
University of Buffalo School of Medicine*	1						1	0	1
Florence*	1						1	0	1
New York University College of Medicine*	1						1	0	1
Munich*						1	0	1	1
Chicago Medical School	1						1	0	1
Tulane University of Louisiana School of Medicine*	1						1	0	1
University of Michigan Medical School*	2						2	0	2
Harvard Medical School*	7						7	0	7
University of Vermont College of Medicine*		1					0	1	1
Columbia University College of Physicians and Surgeons*	3						3	0	3
McGill University Faculty of Medicine*	2						2	0	2
Loyola University School of Medicine*		1					0	1	1
University of Maryland School of Medicine*		1					0	1	1
Rome*		1				1	0	2	2
Athens*						1	0	1	1
Missouri College of Medicine and Science†						1	0	1	1
University of California Medical School*	1						1	0	1
Emory University School of Medicine*	1						1	0	1
University of Virginia Department of Medicine*	1						1	0	1
Frankfort*	1						1	0	1
Masaryk*	1						1	0	1
St. Louis College of Physicians and Surgeons						1	0	1	1
	65	51	6	56	5	47	76	154	230

*Approved schools.
†Osteopathic schools.

Approved schools	50	12^{7}‡	1	4^{3}	0	3^{3}	51	19^{13}	70
Non-approved schools	14	21	4	44	3	39	21	104	125
Osteopathic schools	1	18	1	8	2	5	4	31	35
	65	51	6	56	5	47	76	154	230

‡The exponents represent graduates of European schools.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Theide, former concertmaster with the Cleveland Symphony Orchestra and the Philadelphia Symphony Orchestra, every Thursday at 8:30 p.m., in Studio A, Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic at the Peter Bent Brigham Hospital will be held on Wednesday, December 20, from 2 to 4 p. m. Drs. Elliott C. Cutler and Soma Weiss will speak on "Jaundice." A clinicopathological conference, conducted by Dr. Elliott C. Cutler, will take place from 4 to 5 p.m.

On Thursday, December 21, from 8:30 to 9:30 a.m. there will be at the Peter Bent Brigham Hospital, a combined clinic, conducted by Dr. Elliott C. Cutler, of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital.

Physicians and students are cordially invited to attend.

ELLIOTT C. CUTLER, M.D., *Secretary.*

MASSACHUSETTS DEPARTMENT OF CIVIL SERVICE AND REGISTRATION

MEDICAL ADVISER, DEPARTMENT OF INDUSTRIAL ACCIDENTS

Director of State Civil Service, Ulysses L. Lupien, has recently announced that a competitive examination is to be held on January 6 to find eligibles for appointment to the position of Medical Adviser, Department of Industrial Accidents. The minimum salary is $4200 a year; the maximum, $5100. The duties are as follows: to examine medical testimony given by physicians and technicians at formal proceedings; to make physical examinations of injured workmen and submit opinions and diagnoses as to disability and causal relation to injury; to advise the Industrial Accident Board as to the selection of competent industrial-disease referees and impartial physicians; to interpret medical problems and terminology for the members of the Board; to systemize and supervise the personnel of the medical unit of the department. The appointees will be permitted to carry on private practice to such extent as is approved by the Department of Industrial Accidents.

The entrance requirements are as follows: applicants must be physicians licensed to practice medicine by the Massachusetts Board of Registration in Medicine and must be or must have been members of the medical or surgical staff of a hospital approved by the American College of Surgeons.

The subjects and weights are as follows: training and experience, 2; practical questions, 3; total, 5. Applicants must obtain at least 70 per cent in each subject of the examination in order to become eligible. Physical fitness is to be determined by physical examination.

The last date for filing applications is Saturday, December 23, 1939, at noon.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The annual meeting of the New England Society of Physical Medicine will be held on Wednesday evening, December 20, at the Hotel Kenmore, Boston. An informal dinner will be held in the Empire Room at 6:30.

PROGRAM

Tumor Formation in the Mineral, Vegetable and Animal Kingdom (illustrated by slides). Dr. William S. Bainbridge. Discussion by Drs. Halsey B. Loder and William D. McFee.

All members of the medical profession are cordially invited to attend.

WILLIAM D. MCFEE, M.D., *Secretary.*

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The seventeenth annual meeting of the American Orthopsychiatric Association, an organization for the study and treatment of behavior and its disorders, will be held at the Hotel Statler, Boston, on February 22, 23 and 24, 1940.

NORVILLE C. LAMAR, *Secretary.*

UNITED STATES CIVIL SERVICE COMMISSION EXAMINATIONS

Junior Medical Officer (rotating internship), $2000 a Year
Junior Medical Officer (psychiatric resident), $2000 a Year

The place of employment is to be St. Elizabeths Hospital, Department of the Interior, Washington, District of Columbia. Applications for these positions must be on file with the United States Civil Service Commission, Washington, District of Columbia, not later than January 2.

For the position of Junior Medical Officer (rotating internship) applicants must be fourth-year students in a Grade-A medical school. For the position of Junior Medical Officer (psychiatric resident) applicants must have successfully completed four years of study in a Grade-A medical school subsequent to December 31, 1936, and they must have successfully completed an internship of at least one year, provided that applications will be accepted from persons now serving an accredited rotating internship.

Full information regarding these examinations may be obtained from the secretary of the United States Civil Service Board of Examiners, at any first-class post office, from the United States Civil Service Commission, Washington, District of Columbia, or from the United States Civil Service district office at Boston.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, DECEMBER 18

MONDAY, DECEMBER 18

*12:15 p.m.–1:15 p.m. Clinicopathological conference. Dr. S. Burt Wolbach, Peter Bent Brigham Hospital amphitheater.

*8:15 p.m. New England Heart Association. Peter Bent Brigham Hospital.

TUESDAY, DECEMBER 19

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

*12 m. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15 p.m.–1:15 p.m. X-ray conference. Dr. Merrill C. Sosman. Peter Bent Brigham Hospital amphitheater.

WEDNESDAY, DECEMBER 20

*12 m. Clinicopathological conference. Children's Hospital amphitheater.

*2 p.m.–4 p.m. Joint medical and surgical clinic. Peter Bent Brigham Hospital.

8:15 p.m. Boston Lying-in Hospital.

THURSDAY, DECEMBER 21

*8:30 a.m.–9:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

FRIDAY, DECEMBER 22

*10 a.m.–12:30 p.m. Boston Dispensary tumor clinic.

*Open to the medical profession.

DECEMBER 15 — New England Roentgen Ray Society. Page 917, issue of December 7.

DECEMBER 15 — Waltham Hospital. Clinicopathological conference. Page 880, issue of November 30.

DECEMBER 15 — Boston Dispensary. Clinical staff meeting. Page 916, issue of December 7.

DECEMBER 15 — United States Marine Hospital. Page 918, issue of December 7.

DECEMBER 18 — New England Heart Association. Page 917, issue of December 7.

DECEMBER 19 — South End Medical Club. Page 917, issue of December 7.

DECEMBER 20 — Boston Lying-in Hospital. Page 917, issue of December 7.

DECEMBER 20 — Jewish Memorial Hospital. Page 956.

DECEMBER 20 — New England Society of Physical Medicine. Page 957.

DECEMBER 20 — Peter Bent Brigham Hospital. Joint medical and surgical clinic. Page 957.

DECEMBER 21 — Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital. Page 957.

DECEMBER 22 — Waltham Medical Club. Page 880, issue of November 30.

DECEMBER 27 — Metropolitan State Hospital. Clinicopatho'ogical conference. Page 880, issue of November 30.

DECEMBER 29 and 30 — Phi Delta Epsilon. Page 918, issue of December 7.

JANUARY 6, JUNE 8–11, 1940 — American Board of Obstetrics and Gynecology. Page 160, issue of July 27, and page 798, issue of November 16.

JANUARY 11 — Pentucket Association of Physicians. 8:30 p.m., Hotel Bartlett, Haverhill.

JANUARY 22–25, 1940 — American Academy of Orthopaedic Surgeons. Hotel Statler, Boston.

FEBRUARY 11–14 — International College of Surgeons. Page 759, issue of November 9.

FEBRUARY 22, 23 and 24 — American Orthopsychiatric Association. Page 957.

MARCH 2, JUNE 8 and 10 — American Board of Ophthalmology. Page 719, issue of November 2.

MARCH 7–9, 1940 — The New England Hospital Association. Hotel Statler, Boston.

MAY 14, 1940 — Pharmacopoeial Convention. Page 894, issue of May 25.

JUNE 7–9, 1940 — American Board of Obstetrics and Gynecology. Page 1019, issue of June 15.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 3, 1940 — Semi-annual meeting. Combined meeting with Essex South. Danvers State Hospital, Hathorne. 7 p.m.

ESSEX SOUTH

JANUARY 3, 1940 — "Head Injuries." Dr. John S. Hodgson. Danvers State Hospital, Hathorne.

FEBRUARY 14 — "Cough, Sputum, Hemoptysis — How shall they be investigated?" Dr. Reeve H. Betts. Essex Sanatorium, Middleton.

MARCH 6 — "Experimental and Clinical Considerations of Sulfanilamide Treatment of Hemolytic Streptococcal Infections." Dr. Champ Lyons. Lynn Hospital, Lynn.

APRIL 3 — Addison Gilbert Hospital, Gloucester.

MAY 8 — Annual meeting. Salem Country Club, Peabody.

HAMPSHIRE

JANUARY 10, 1940.

MARCH 13.

MAY 8.

All meetings are held at 11:30 a.m. at the Cooley Dickinson Hospital, Northampton.

MIDDLESEX EAST

JANUARY 10, 1940.

MARCH 20.

MAY 15.

Meetings are held at 12:15 p.m. at the Unicorn Country Club, Stoneham.

MIDDLESEX NORTH

JANUARY 31, 1940.

APRIL 24.

JULY 31.

OCTOBER 30.

NORFOLK SOUTH

JANUARY 4, 1940.

FEBRUARY 1.

MARCH 7.

APRIL 4.

MAY 2.

All meetings, with the exception of one which is usually held at the Quincy City Hospital, are held at the Norfolk County Hospital in South Braintree, at 12 o'clock noon.

PLYMOUTH

JANUARY 18, 1940 — Brockton Hospital, Brockton.

MARCH 21 — Goddard Hospital, Brockton.

APRIL 18 — State Farm.

MAY 16 — Lakeville Sanatorium, Lakeville.

SUFFOLK

JANUARY 31, 1940 — Scientific meeting. Subject to be announced later.

MARCH 27 — Scientific meeting. Symposium on Ulcerative Colitis and Diarrheas. Under the direction of Dr. Chester M. Jones.

APRIL 24 — Annual meeting in conjunction with the Boston Medical Library. Election of officers. Program and speakers to be announced later.

WORCESTER

JANUARY 10, 1940 — Worcester City Hospital.

FEBRUARY 14 — Worcester State Hospital.

MARCH 13 — Worcester Memorial Hospital.

APRIL 10 — Worcester Hahnemann Hospital.

MAY 8 — Worcester Country Club.

Each meeting begins with a dinner at 6:30 p.m. and is followed by a business and scientific meeting.

BOOK REVIEW

Treatment by Diet. Clifford J. Barborka. Fourth edition, revised. 691 pp. Philadelphia, London and Montreal: J. B. Lippincott Co., 1939. $5.00.

The amazing advances in the knowledge pertaining to vitamins have focused attention on problems of diet. The unfortunate economic plight of many has furnished an array of bizarre clinical forms of vitamin deficiencies, and extensive opportunities for therapeutic application of this knowledge have thus become available. The author of this book discusses the vitamins in a succinct yet adequate manner, although the interminable flow of facts cannot be covered by any textbook. His castigation of the exploitation of vitamins over the radio and in other ways, which unfortunately at present is beyond medical control, is well founded.

The book discusses dietetics from three aspects: diet in health; the application of diet therapy; and diet in disease. The greater portion of the book is devoted to tables from which can be culled the appropriate diet under various conditions. Throughout the volume a rational physiological approach is emphasized.

In the section on ulcer therapy one notes the omission of any mention of the Meulengracht regime of early and liberal feeding following hematemesis and melena and of the use of the Andresen gelatin mixture for the same purpose. Out of deference to its originator the Sippy diet should have been reproduced as he devised it; the modifications, however, are sound.

Whether intravenous alimentation by means of amino acids will prove feasible is sufficiently debatable to warrant omission. Too much stress is placed on liver as such in the treatment of pernicious anemia; the various extracts have demonstrated their merit and convenience. The reviewer doubts that allergists would place hay fever, as we know it, in the food-allergy group.

Since most medical schools offer insufficient detailed instruction in dietetics, a volume of this type is valuable. Furthermore it will undoubtedly be of use to the practitioner for daily reference.